

Extraction of the Hemodynamic Response Function and Parameter Estimation for the Two Gamma Difference Model

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Abstract

When certain regions of the brain are stimulated, the activation induces a change in the concentration of oxygen in that portion of the brain. The nature of this hemodynamic response is a very important component of understanding brain function. The goal of this article is to find the best method of ascertaining the characteristics of the hemodynamic response from an fMRI time series. The structure of the hemodynamic response, referred to as the hemodynamic response function (HRF), can be estimated without assuming any mathematical form or by estimating the parameters of an appropriate model. Four nonparametric methods of extracting the HRF are considered and compared using simulation methods. These four methods – extraction by deconvolution, Wiener filter extraction, LS-F extraction, and LS-T extraction – produce a time series that is a nonparametric estimate of the HRF. There are five methods of parametric estimation of the HRF considered in this article. These include the Convolved HRF fit to the original fMRI time series, and a parametric model fit to the time series resulting from each of the four nonparametric extraction methods. These methods are also compared using simulation methods. It is shown that, in most cases, the LS-T extraction provides the most desirable nonparametric estimation of the HRF, while the Convolved HRF fit provides the best parametric model fit.

1 Introduction

Localized brain activity is detected through the Blood Oxygen Level Dependent (BOLD) effect in fMRI experiments. Magnets in fMRI scanners generate a magnetic field which causes protons in the hemoglobin of the blood, which contains iron, to line up. The amount by which the hemoglobin protons line up with the magnetic field depends on whether oxygen is bound to the hemoglobin. Deoxyhemoglobin, which does not have oxygen bound to it, lines up with the magnetic field much easier than does oxyhemoglobin, since oxygen dampens the net tissue magnetization in the magnetic field (Jezzard 2001). When a part of the brain becomes activated, oxygen consumption from the blood in that area results in an increase in deoxygenated hemoglobin. The magnetic properties of oxygen and hemoglobin allow the fMRI scanner to obtain a measure of changes in the level of blood oxygenation over time. The Hemodynamic Response Function (HRF) is a mathematical characterization of the change in blood oxygenation subsequent to activation (Jezzard 2001).

In order to obtain estimates of the HRF, extraction methods will be investigated and compared under simulation of fMRI signals with different stimulus patterns. Section 2 discusses four different methods of extracting the HRF from the fMRI signal. Section 3 discusses parametric model fitting techniques. Section 4 describes the simulations and Section 5 summarizes the simulation results graphically and numerically. Conclusions are drawn in Section 6. The appendix contains relevant portions of computer code written in R.

2 Extraction of the HRF

Estimates of the HRF can be made with knowledge of only the fMRI signal and the stimulus sequence. No knowledge of any parameterized functional form of the HRF is required to extract an estimate of the HRF. The fMRI time series can be thought of as a convolution of the HRF and the stimulus function, i.e.

$$y(t) = h(t) \otimes x(t) + \eta(t), \quad (1)$$

where t is time, $y(t)$ is the fMRI signal, $\eta(t)$ is random noise, $h(t)$ is the HRF, $x(t)$ is the stimulus function, and \otimes is the linear convolution operator, i.e. $y(t) = \sum_n h(n)x(t-n) + \eta(t)$. The stimulus function, $x(t)$, is a delta function with impulses at the time points at which the stimuli are applied. Using the corresponding capital letter to denote the Fourier transform (FT) in the

frequency domain, the FT of the response function is

$$Y(\omega) = H(\omega)X(\omega) + N(\omega), \quad (2)$$

where ω is frequency. Thus, the original fMRI signal, $y(t)$ (in the time domain), is the inverse FT of $Y(\omega)$, in (2). Since fMRI data have a discrete time domain, the Discrete Fourier Transform (DFT) is used in calculation and given by $X(\omega) = \sum_{j=0}^{n-1} x(j) \exp\left\langle -2\pi i \omega j / n \right\rangle$, where n is the number of time points in the observed signal. The DFT in the time domain and the Inverse DFT in the frequency domain can be calculated efficiently with the Fast Fourier Transform (FFT).

The appendix contains R functions for all of the methods of HRF extraction discussed in the following sections.

2.1 Extraction of the HRF by Deconvolution

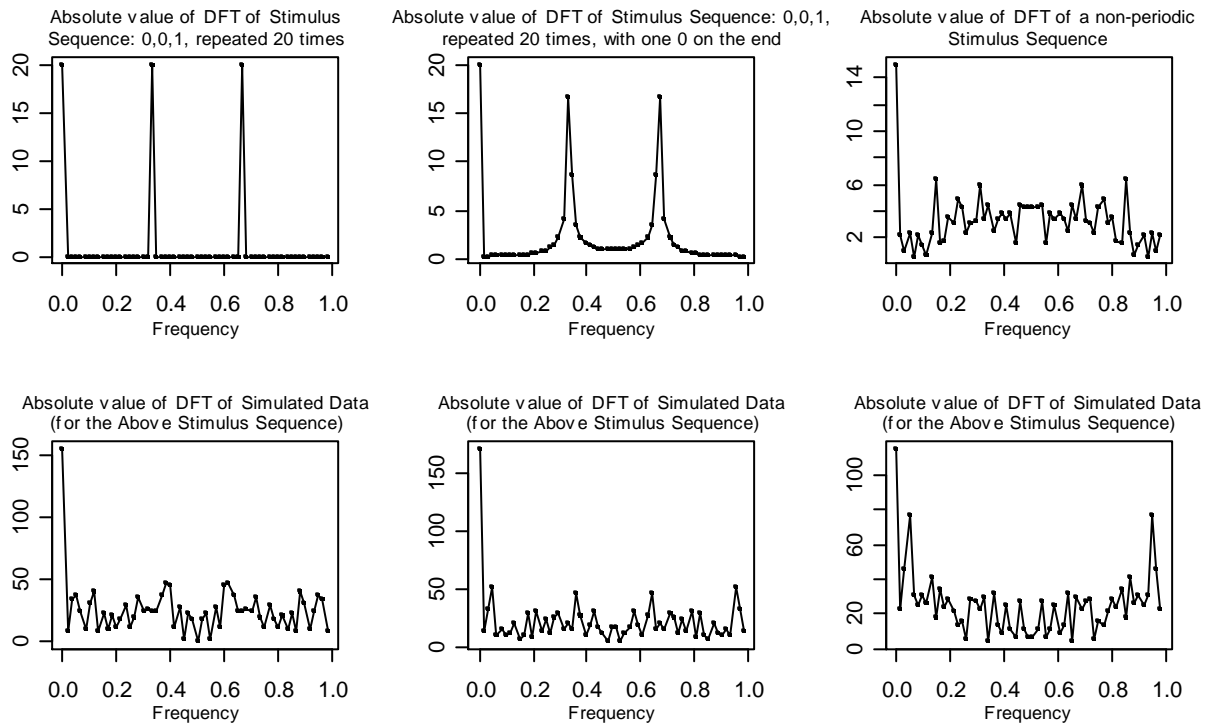
Three of the methods of obtaining the HRF discussed here operate in the frequency domain, using the FFT of the signal and stimulus. The first method deconvolves the stimulus function from the fMRI signal by utilizing the relationship in (2) in the most obvious manner. That is, since $Y(\omega)$ and $X(\omega)$ are known, the deconvolved HRF can be estimated as the inverse FT of

$$\hat{H}_D(\omega) = \frac{Y(\omega)}{X(\omega)} \quad (3)$$

given that none of the $X(\omega)$ are 0. In practice, a zero denominator can present a problem when periodic stimuli are considered. For a discretely sampled function, such as the stimulus function for an fMRI experiment, the Fourier coefficients are evaluated at the harmonics, i.e. integer multiples of the fundamental frequency, $\frac{1}{N}$, where N is the number of sampled time points.

This means that the DFT of the stimulus function will contain zeroes when there is no signal present at any of the frequencies: $0, \frac{1}{N}, \frac{2}{N}, \dots, \frac{N-1}{N}$. This will happen when, for example, the stimuli follow the following pattern: 0,0,1,0,0,1. In this case, the number of sampled points is a multiple of the period of this pattern and all of the stimulus function is contained in the frequencies $1/3$ and $2/3$. This means that the Fourier coefficients for the other frequencies are zero. This presents a problem of division by zero for the deconvolution in (3). Because these frequencies are multiples of the fundamental frequency, they will be evaluated in the DFT since

Figure 1: Instability of the deconvolution for periodic stimulus sequences



$N=6$. In order to solve this problem, one more item in the sequence could be added so that $N=7$ and the stimulus function will not be completely contained in just a few of the DFT frequencies. In a practical sense, whether in a real experiment or in simulation, it is easy to add a zero to the end of a stimulus sequence when a periodic stimulus pattern is desired. There are other stimulus sequences that may not appear periodic, but still may have zero DFT coefficients. One way to guarantee that none of the DFT coefficients are zero is to always let N be a prime number, or N and any stimulus period be relatively prime.

Simulation results indicate that deconvolution does not seem to be able to produce a good estimate of the HRF, especially for periodic stimulus sequences. Figure 1 demonstrates the reason for the deconvolution method's inadequacy. The graph of the absolute value of the DFT of the exactly periodic sequence (top left) shows many Fourier coefficients that are exactly zero. The graph of the DFT of the periodic sequence with one zero added on the end (top middle) has many Fourier coefficients that are close to zero. The graph of the DFT of the non-periodic sequence (top right) has very few Fourier coefficients that are close to zero.

Recalling that the deconvolution method requires dividing the DFT of the data (bottom row of Figure 1) by the DFT of the stimulus sequence (top row), it should not be surprising that

the ratio of the Fourier transforms, and thus the deconvolution, is unstable for the periodic stimulus sequences. Noting the vertical scale of graphs on the bottom row of Figure 1, deconvolution of this periodic stimulus sequences requires division of numbers with absolute values around 25 or 30 by numbers with absolute values below 0.5, resulting in a highly volatile deconvolved HRF that does not look anything like the HRF from which the data were generated.

In the implementation of the deconvolution, the Fourier coefficients were forced to a minimum threshold when they were too close to zero (or equal to zero). This reduces, but does not eliminate, the high volatility of the HRF deconvolved from fMRI signals with highly periodic stimulus patterns. It will be illustrated in simulation that this instability does not appear for non-periodic stimulus sequences.

2.2 Extraction of the HRF using a Wiener Filter

Wiener filtering is a common method to overcome some of the problems of deconvolution mentioned in the previous section. In (3), $\frac{1}{X(\omega)}$ can be thought of as an inverse filter convolved with the “data”, $Y(\omega)$, in order to obtain $\hat{H}_D(\omega)$. The Wiener filter is an inverse filter that also operates as a noise filter. This method actually contains two filters, a denoising filter and an inverse filter. The inverse filter used here is more sophisticated than what was used for deconvolution in Section 2.1. Refer to Glover (1999) and Miller *et al.* (2006) for a discussion of the theory and methods of the implementation of the Wiener filter. Under the assumption that white Gaussian noise is added to the fMRI signal, the Wiener filter achieves optimal denoising by minimizing the mean square error between the extracted and true signals.

In the frequency domain, the Wiener filter estimate of $H(\omega)$ is

$$\hat{H}_w(\omega) = \frac{X^*(\omega)Y_s(\omega)}{|X(\omega)|^2 Y_s(\omega) + N_s(\omega)} \quad (4)$$

where the superscript $*$ denotes complex conjugate, $Y_s(\omega)$ and $N_s(\omega)$ are the spectral density estimates of the observed fMRI signal and the noise, from (1), at frequency ω . The inverse and optimal denoising filters can be seen clearer when $H(\omega)$ is rewritten as

$$\hat{H}_w(\omega) = \left[\frac{1}{X(\omega)} \right] \frac{|X(\omega)|^2}{|X(\omega)|^2 + N_s(\omega)/Y_s(\omega)}. \quad (4)$$

Note that $N_s(\omega)/Y_s(\omega)$ is the reciprocal of the signal to noise ratio at frequency ω . The inverse filter, $\frac{1}{X(\omega)}$, is the same one as in the deconvolution method. The denoising filter “tunes” itself based on the signal to noise ratio at each frequency. Clearly, if there were no noise in the data, the signal to noise ratio would be infinite and the filter would simply be an inverse filter.

In order to achieve the best possible noise filtering, it is necessary to find a good estimate for the noise. Most implementations of the Wiener filter assume a Gaussian white noise structure. This means that the noise spectrum is constant, i.e. $N_s(\omega)$ is simply the constant estimate of the variance of the noise. In an fMRI experiment, it would be possible to wait several seconds before the first stimulus and use the pre-stimulus signal to estimate the variance of the noise. But, as this pre-stimulus signal may not always be available, the noise could also be approximated from voxels in the brain determined to be unaffected by the stimuli. Either of these noise variance estimates could be used with real fMRI data, but the estimate used in the simulations reported here is the true value of the variance of the distribution from which the random noise was generated.

2.3 LS-F Extraction of the HRF

An alternative technique for extracting the HRF in the frequency domain also takes advantage of the relationship in (2). This method was introduced by Ari *et al.* (2001) as an HRF extraction method that is robust to varying Inter-Stimulus Intervals. Consider the equality

$$Y(\omega) - H(\omega)X(\omega) = 0 \quad (5)$$

which is algebraically the same as (3). But instead of forcing the expression to zero, a least squares solution,

$$\min_{h_{32}(t)} \|Y(\omega) - \text{DFT}[h_{32}(t)]X(\omega)\|^2, \quad (6)$$

can be found. This minimization is with respect to the HRF, $h_{32}(t)$, in the time domain so that an inverse Fourier transformation is not required. The notation $h_{32}(t)$ is used to emphasize the fact that the parameters of this minimization are the time points of $h_{32}(t)$, which corresponds to an

HRF for which time points beyond 32 seconds are set to zero. This is done because it appears that the physiological extent of the HRF is no more than 32 seconds. If those values were not forced to zero, the expression inside the modulus in (6) would reduce to the expression in (5).

Since the HRF is extracted under a Least Squares criterion in the frequency domain in this method, it will be referred to as LS-F extraction. While the LS-F extracted HRF is observed to be less volatile than the deconvolved HRF under simulation, it still has problems extracting the HRF from the error-free HRF convolved with a periodic stimulus sequence. Since the DFT of the stimulus function is involved in LS-F extraction as in the deconvolution, the LS-F extraction method is also subject to instability due to multiplying by Fourier coefficients that are close to zero. Because of this, the Fourier coefficients were forced to a minimum threshold, as in the deconvolution.

2.4 LS-T Extraction of the HRF

Because of the difficulty of working in the frequency domain, a method for extracting the HRF in the time domain is investigated. The method is very similar to the LS-F extraction in that it uses a least squares criterion to extract the first 32 seconds of the HRF. The difference is that it uses a convolution operator in the time domain. The least squares minimization criterion for extracting the HRF in the time domain becomes

$$\min_{h_{32}(t)} \left\{ \sum_{j=0}^{31} \left(x(j) - \sum_{i=0}^{j-1} h_{32}(i) x(j-i) \right)^2 \right\}, \quad (7)$$

which will be denoted LS-T. Because the convolution used here is a linear operator, this minimization problem becomes a linear regression problem where each time point of the HRF is a parameter for which a least squares estimate can be calculated easily.

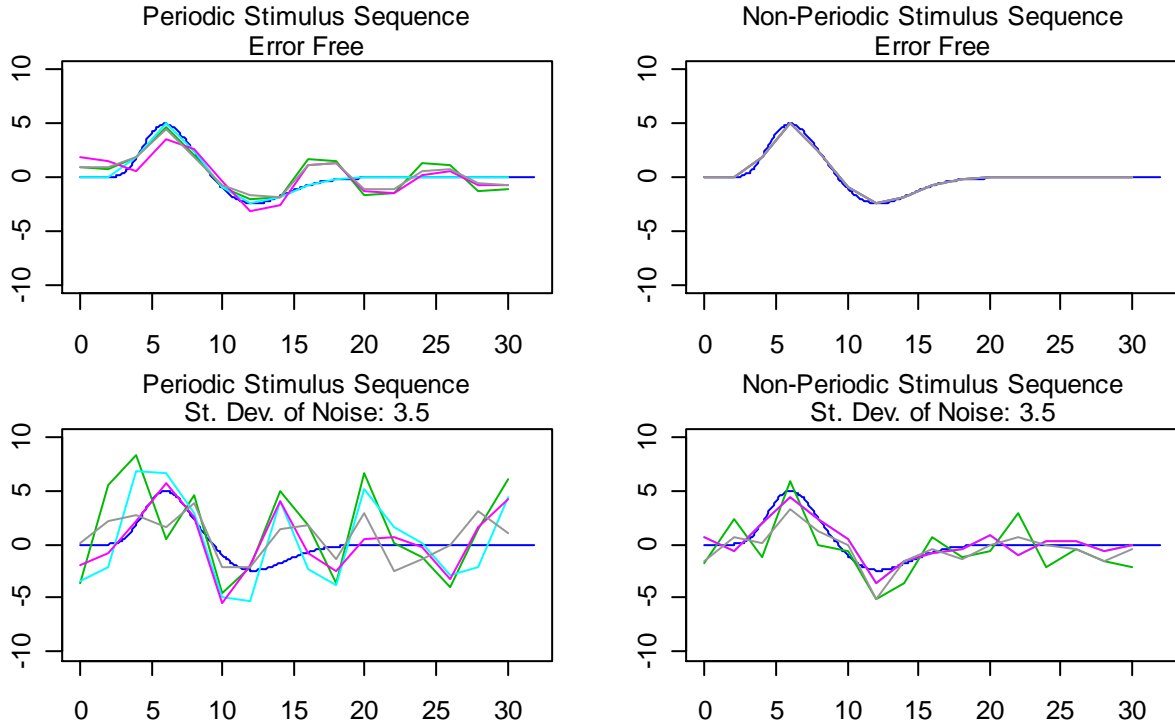
Intuitively, the advantage of this method over LS-F is that the numerical instability caused by multiplication and division by small numbers in the frequency domain is avoided altogether. It should be noted that this method uses efficient linear regression methods to extract the HRF, whereas LS-F requires a much slower nonlinear optimization routine.

2.5 Comparison of the Extracted HRF's

Figure 2 shows the three extracted HRF's for four different stimulus sequences. The extracted HRF's are compared for periodic (left column) and non-periodic (right column)

Figure 2: Extraction Methods for Periodic and Non-Periodic Stimulus Sequences

Color Key: True HRF (blue), Deconvolved HRF (green), LS-T Extracted HRF (light blue), LS-F Extracted HRF (purple), HRF from Wiener Filter (grey)



stimulus sequences, with error-free (top row) and noisy (bottom row) simulated data. The best extracted HRF is the one that most closely follows the true HRF (blue) from which the data were simulated. It should be noted that the Wiener filter extraction is at least as good as the deconvolution in these graphs. Notice also that the LS-F extracted HRF (purple) also has problems with the error-free data simulated from a periodic stimulus sequence, where the LS-T (light blue) follows the true HRF very closely. When noise is added, however, the LS-F extraction is actually less volatile than the LS-T extraction. The LS-T and LS-F methods produce very similar extracted HRF's for the error-free and noisy data simulated from the non-periodic stimulus sequence. This is difficult to see from Figure 2 because the curves of the extracted HRF's from those methods are overlapping.

III. Model Fitting Techniques

Because of the noisy nature of fMRI data and the HRF extracted from it, it is desirable to fit a smooth curve to the data or the HRF in order to learn more about the shape of the HRF and

to detect activation. It has been shown that a 6 parameter difference of two gamma functions often can model the HRF fairly well (Friston *et al.* 1998). The parameters for this model can be estimated through nonlinear least squares minimization.

Parameter estimation for this model will fall into two categories. In one category, the least squares minimization would be with respect to the sum of squared differences, or residuals, at each time point between the fitted HRF model convolved with the stimulus function and the observed, or simulated, data. This parameter estimation, which will be referred to as the convolved HRF fit, was performed by Lin (2006) by minimizing the sum of squared residuals between the HRF convolved with the stimulus sequence and the observed fMRI time series. In the other category, the residuals of the two-gamma-difference model fit to the *extracted* HRF's are minimized. There are 4 methods that fall in this category, one for each method of HRF extraction.

The primary goal of this simulation is to determine the best method to fit the HRF among fitting the convolved HRF, the deconvolved HRF, the LS-F extracted HRF, the LS-T extracted HRF, and the extraction using the Wiener filter. The quality of each of these five methods will be assessed based on simulation and how well each fit agrees with the model from which the data were simulated. While finding the best method of fitting the observed fMRI data is of most importance, it is also valuable to find the best extraction method without fitting any parameterized HRF model.

IV. Simulation Details

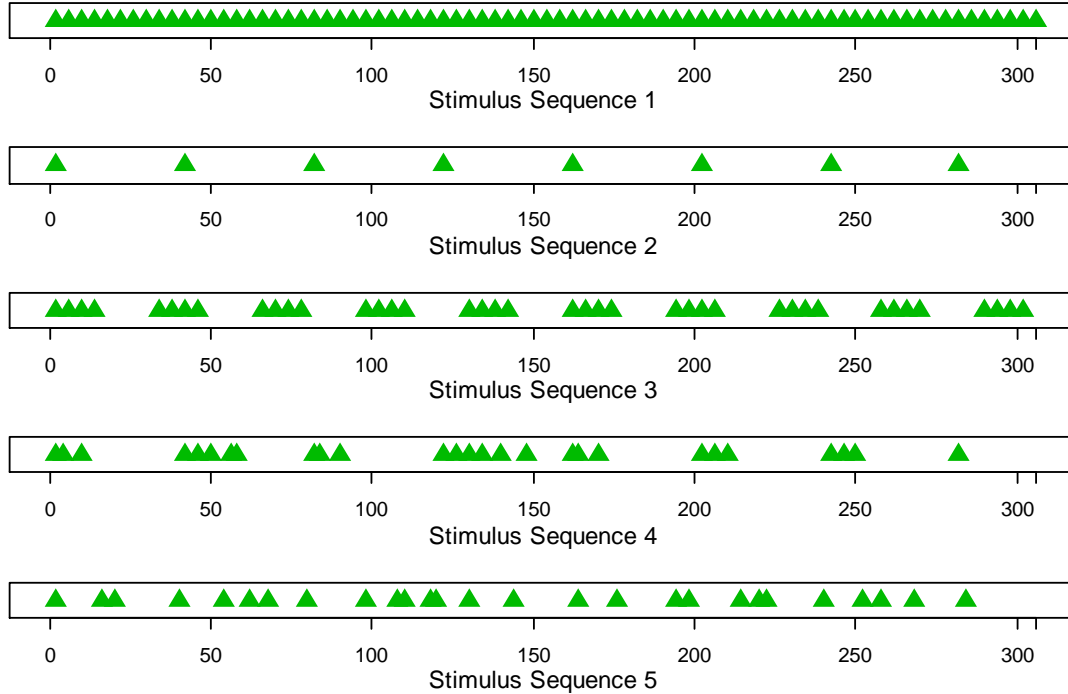
This section gives details of the simulations carried out to obtain the results given in the following section. The underlying model for HRF is the two-gamma-difference model with the functional form given in (8).

$$h(t) = c_1 \left\{ \left[\frac{t}{d_1} \exp\left(\frac{-t-d_1}{d_1}\right) \right]^{a_1} - c_2 \left[\frac{t}{d_2} \exp\left(\frac{-t-d_2}{d_2}\right) \right]^{a_2} \right\} \quad (8)$$

The parameters used for this simulation were: $a_1 = 13, a_2 = 27, d_1 = 6, d_2 = 12, c_1 = 5, c_2 = 0.5$.

These parameters are reasonable based on preliminary unpublished work. This HRF was convolved with 3 periodic stimulus sequences – one with the stimulus applied every 4 seconds, another with the stimulus applied every 20 seconds, and another with clusters of 4 stimuli with

Figure 3: Stimulus Sequences for the Simulation.



20 seconds of rest in between clusters – and 2 non-periodic sequences – one with clusters and one without clusters. See Figure 3 for graphical representation of each stimulus sequence. Gaussian white noise was then added, having standard deviation from 0 (error-free model) to 5 (very noisy model). Whether using the convolved or an extracted HRF, the non-linear least squares minimization attempts to find the parameters that minimize the sum of the squared residuals from the model fit. The parameters were estimated using the function `optim`, a variable metric optimization algorithm in R (2007). These parameters were then compared with the parameters from which the data were originally simulated. As another means of comparison, the sum-of-squared residuals of the model fit were calculated. A small sum-of-squared residuals would indicate that the model follows the simulated data well. While this is a useful measure, it is of more interest to see how closely each fitted HRF follows the actual HRF. So a sum of squared errors (SSE) of the fitted HRF from the true HRF was calculated as well. Furthermore, the correlation of the fitted HRF with the true HRF was calculated as one more measure of the quality of the model fit.

With no parameter constraints and trivial starting values (such as each parameter starting at a value of 1), a least squares minimization routine could produce parameter estimates that give

a very unrealistic picture of the HRF. It is more desirable to take advantage of the physiological properties of the HRF and make adjustments to avoid poor parameter estimates as much as possible. The parameter d_1 can be physiologically interpreted as the time from the stimulus to the peak of the HRF. Similarly, d_2 is the time to the valley of the HRF. Since the increase in the concentration of deoxyhemoglobin precedes the dip below the baseline level, d_2 should be greater than d_1 if the two-gamma-difference model is appropriate. So this parameter constraint was included in the optimization routine.

The complicated nature of this 6-dimensional fitting procedure requires care in choosing the starting values for the parameters. A popular software package called Statistical Parametric Mapping (SPM) specifies the following values as its default parameter values for the two-gamma-difference model: $a_1=6$, $a_2=12$, $d_1=5.4$, $d_2=10.8$, $c_1=5$, $c_2=0.35$. These were the starting values for the parameters with one exception. The maximum of the observed HRF (extracted or convolved) was used for the starting value of c_1 . These specifications for the optimization were recommended and used by Lin (2006).

Even with these constraints and starting values, problems with the fit persisted in many circumstances. While a poor set of parameter estimates could be the result of a poor extraction or the result of an HRF from certain stimulus sequences being too difficult to fit, the goal here was to avoid a poor fit when the observed HRF looked reasonable. If the resulting fit did not meet the criteria for being a realistic HRF, the optimization was repeated with different starting parameter values, up to six times. There were four criteria that had to be met for the model fit to be considered adequate. These criteria appeared to be appropriate for this simulation. The first criterion is that the d_1 parameter had to be between 1 and 16. Second, the d_2 parameter had to be between 2 and 30. These ranges more than cover the reasonable values for those parameters, indicating that parameters outside of those ranges would provide a poor model fit. The third criterion is that no individual residual from the model fit could exceed a certain absolute value (6 for the extraction methods and 10 for the convolved method). The fourth criterion is that the optimization routine had to converge. Since there could be up to seven different model fits from the seven different sets of starting values for each method in each realization of the simulation, the convergent model fit with the smallest sum-of-squared residuals was chosen to include in the summary statistics.

V. Summary of the Simulation Results

This section contains various graphical and numeric summaries of the simulation. The graphs have a color code for each method with a key at the top (WF stands for Wiener Filter in the graphs). Section 5.1 contains several graphs of extracted HRF's and two-gamma-difference model fits. Section 5.2 contains a summary of the performance of the extracted HRF's from the 4 extraction methods, without fitting any model. Section 5.3 summarizes the quality of the fitted models from each of the 5 fitting methods.

5.1 Plots of Extracted and Fitted HRF's

Figures 4-8 represent typical extracted HRF's and two-gamma-difference model fit to the data simulated from each of the 5 stimulus sequences. The upper plot of each figure has a typical plot of the noisy simulated data and the fitted HRF from each method convolved with the corresponding stimulus sequence. The stimulus sequence (green triangles) is shown at the bottom of this plot for convenience. The lower two plots show the estimated HRF's, not convolved with the stimulus sequence. The lower left plot contains the extracted HRF's. Note that the convolved HRF does not have an associated extraction method, so it is not included in the lower left plots. The lower right plot graphs the fitted two-gamma-difference model. All plots show the true, error-free HRF for comparison. The best method of extraction or parameter estimation is the one whose HRF curve follows closest to the error-free curve. The standard deviation of the noise added to the convolved signal in these graphs was chosen to be 3.5 because this magnitude of error is similar to the errors found in a preliminary unpublished fMRI experiment. As many of the extracted and fitted HRF's are indistinguishable in many of the plots, dots are placed on the graph to more clearly identify the various HRF estimates.

It seems clear that the deconvolution method has a very poor HRF extraction for the highly periodic stimulus sequences 1, 2, and 3. This is not unexpected considering the discussion in Section 2. The fit of the two-gamma-difference model is not as poor, but is worse than for any other method. The Wiener filter performed comparably to the LS-T and LS-F methods while being much better than the deconvolution method. The convolved fit seems to consistently follow the true, simulated HRF very well. This is especially true for stimulus sequence 3, where no other method could be considered reasonable. With the exception of stimulus sequence 1, LS-T and LS-F behave very similarly. The similarities should not be

surprising since they both extract the HRF under a minimized sum of squares criterion.

Every method of extraction and model fitting for the data simulated from stimulus sequence 1 produced a poor representation of the HRF. A few of the methods cannot properly represent the true HRF very well for sequences 2 and 3. For stimulus sequences 4 and 5, however, it appears that all methods extract an HRF and produce a model fit very close to the true simulated HRF. In general for all methods, the extraction and the model fit perform better for data with stimulus sequences that have stimuli that are irregularly spaced.

Figure 4: Stimulus Sequence 1, St. Dev. of the Noise: 3.5

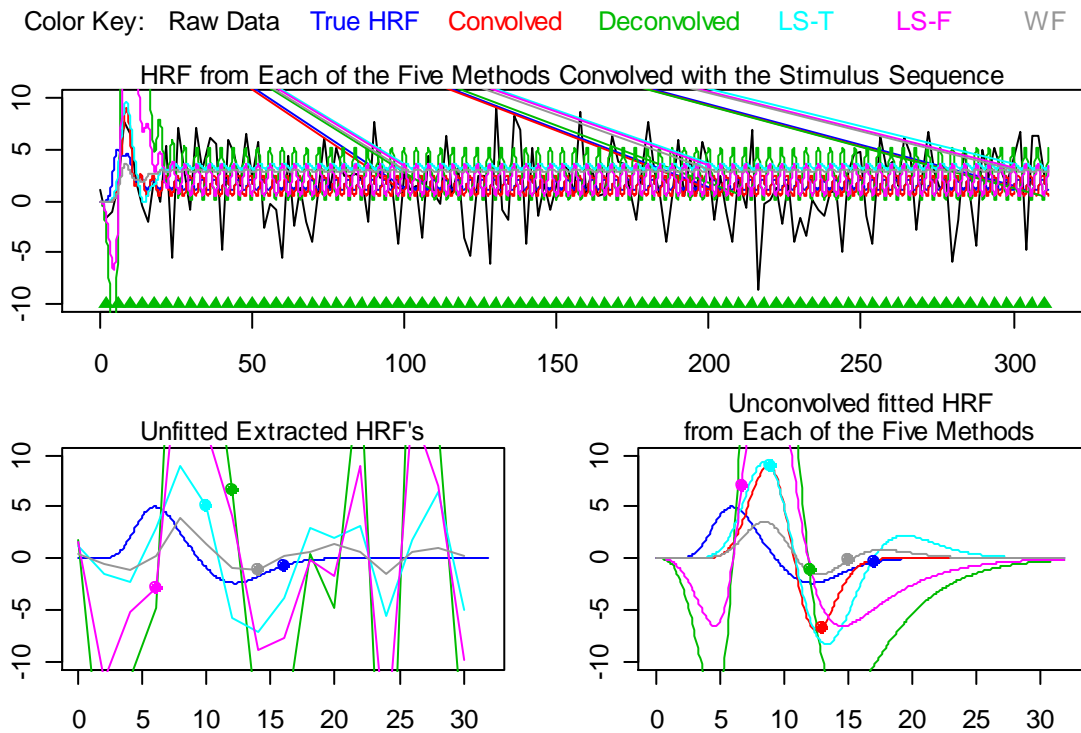


Figure 5: Stimulus Sequence 2, St. Dev. of the Noise: 3.5

Color Key: Raw Data True HRF Convolved Deconvolved LS-T LS-F WF

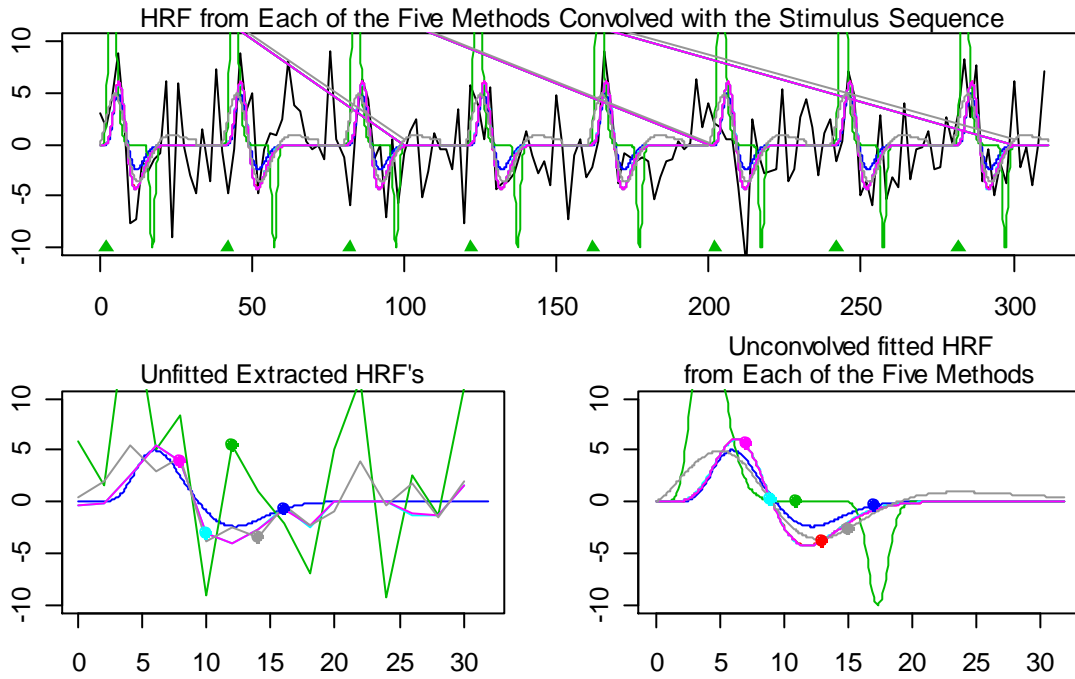


Figure 6: Stimulus Sequence 3, St. Dev. of the Noise: 3.5

Color Key: Raw Data True HRF Convolved Deconvolved LS-T LS-F WF

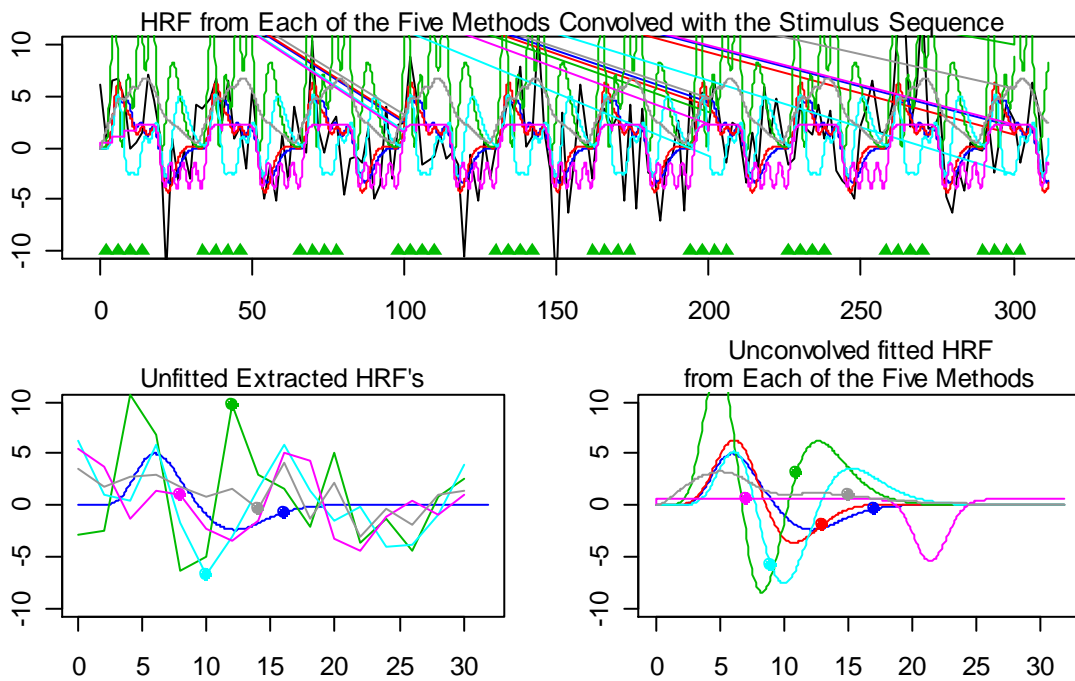


Figure 7: Stimulus Sequence 4, St. Dev. of the Noise: 3.5

Color Key: Raw Data True HRF Convolved Deconvolved LS-T LS-F WF

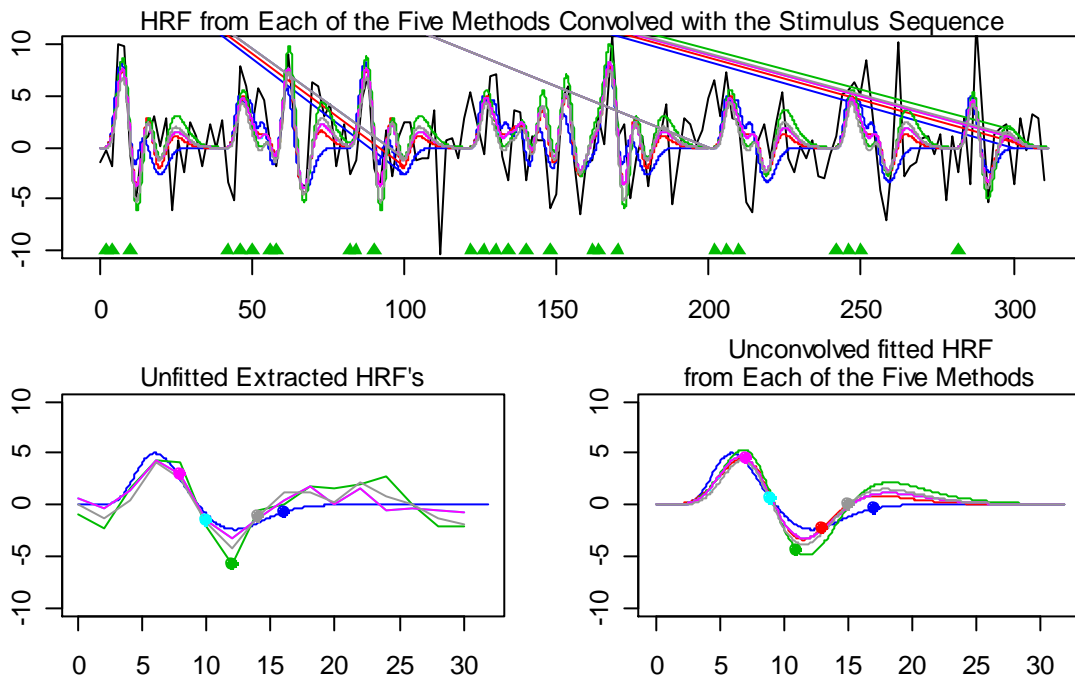
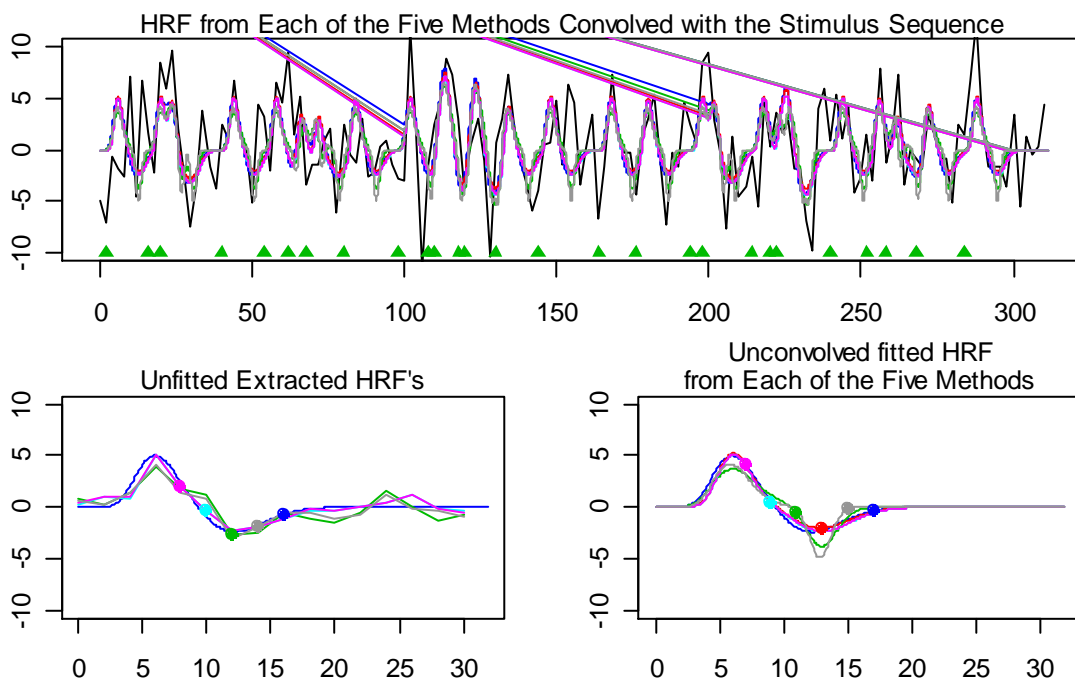


Figure 8: Stimulus Sequence 5, St. Dev. of the Noise: 3.5

Color Key: Raw Data True HRF Convolved Deconvolved LS-T LS-F WF



5.2 Performance of the Extraction Methods (Without Any Fitted Models)

In order to summarize these findings for a large number of simulations, Figure 9 has the SSE of the extracted HRF from the true simulated HRF averaged over all runs of the simulation plotted against the standard deviation of the noise. Obviously, a smaller SSE is better and the lowest curve is the best one. Figure 10 has the average correlation of the extracted HRF with the true HRF plotted against noise standard deviation, with the highest curve being best. It is important to investigate these statistics for a range of noise variance since the nature of fMRI noise is not fully understood. It is also important to use both of these quantities in order to get an accurate assessment of similarity between the extracted HRF's and the true HRF. For example, Figure 9 shows a relatively low SSE for the extracted HRF from the Wiener filter for data simulated from stimulus sequence 1. However, Figure 10 shows a very small correlation with the true HRF for the Wiener filter extracted HRF in the same stimulus sequence. This behavior is demonstrated in Figure 4, indicating that the extracted HRF has low variability but fails to closely follow the true HRF, because it is flatter and shifted to the right compared to the true HRF. For this reason, both the SSE and correlation are important quantities for assessing the quality of the model fit.

Figure 9: Average SSE of Extracted HRF from True HRF, based on 1000 simulations

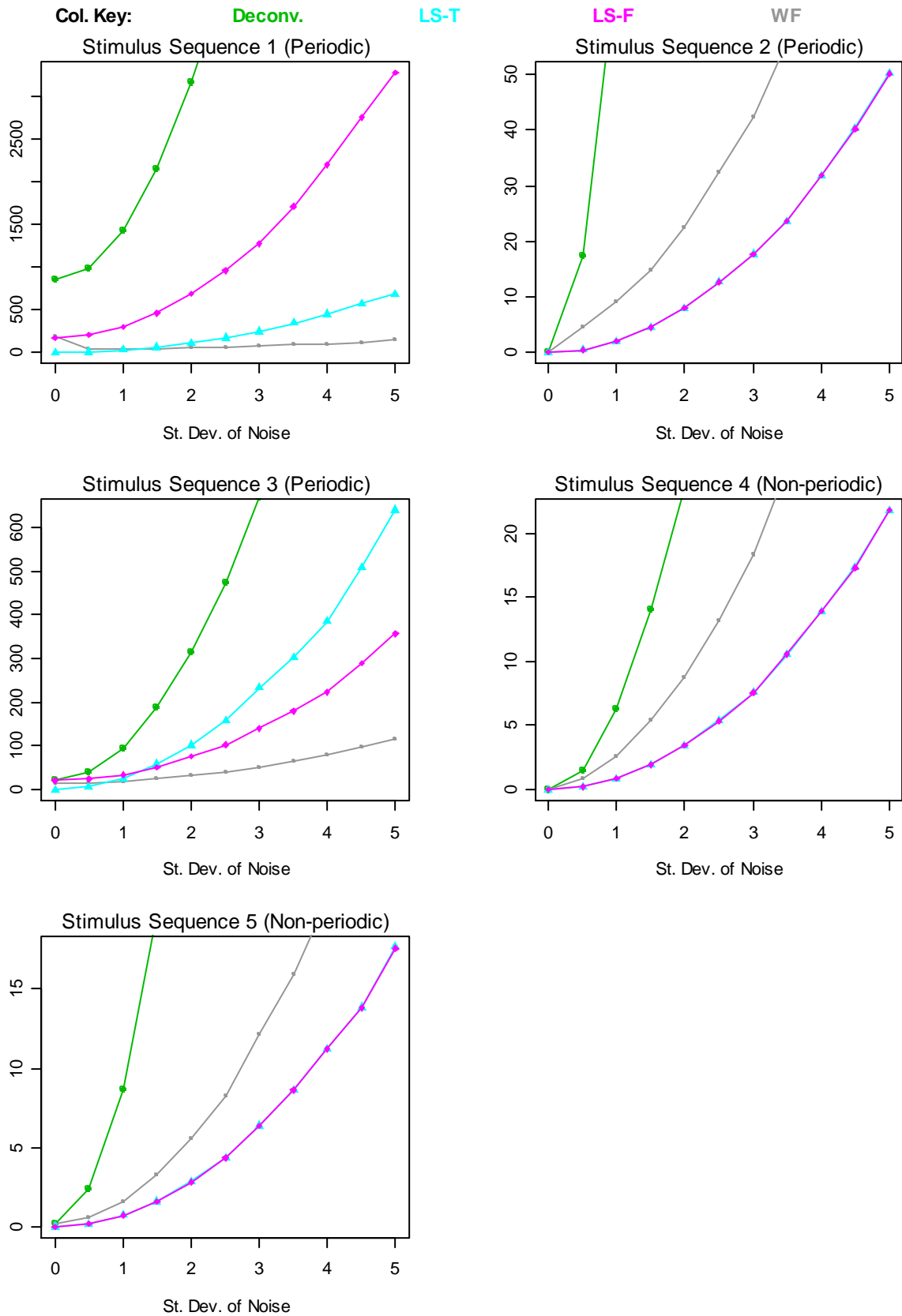
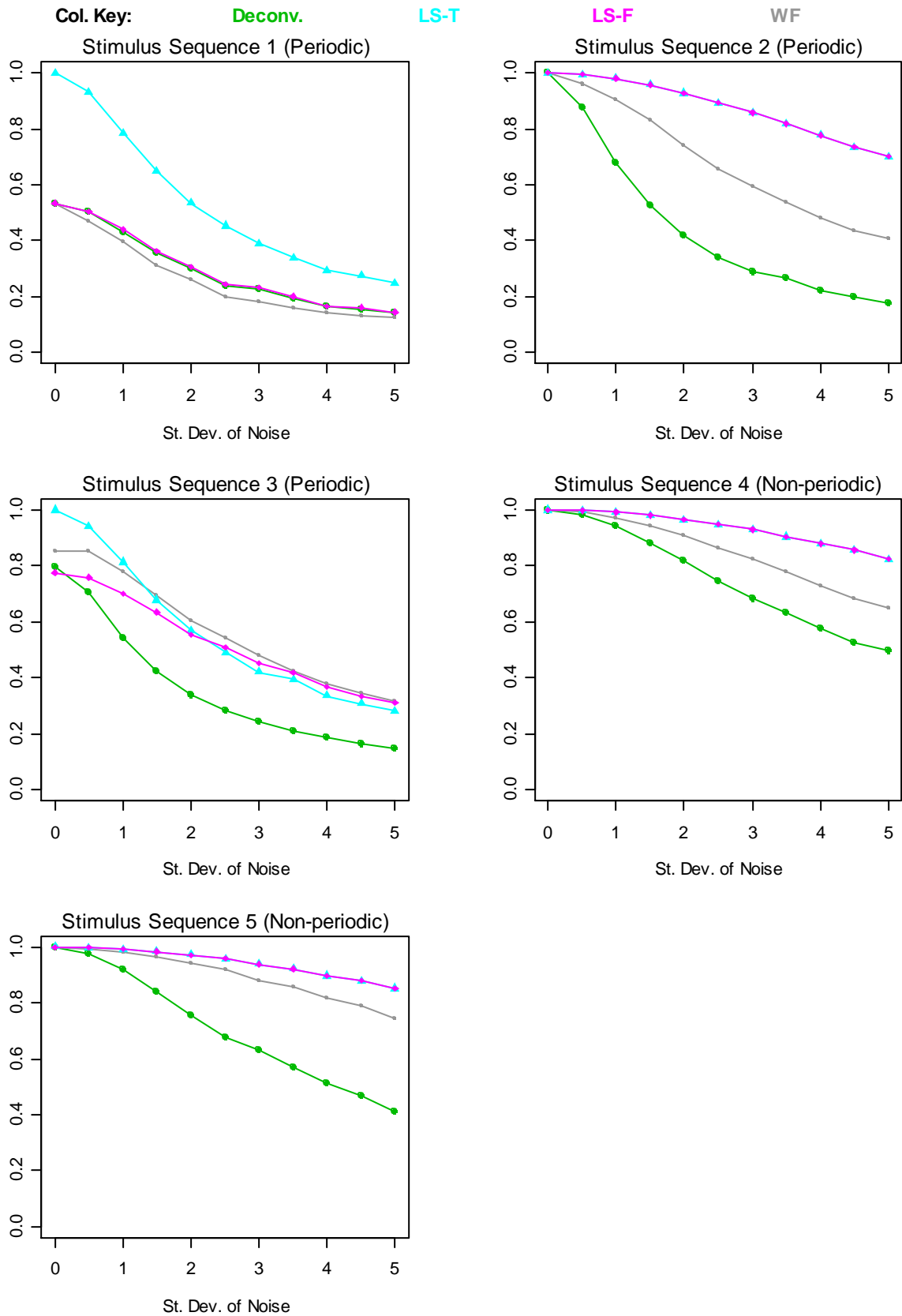


Figure 10: Average Correlation of Extracted and True HRF, based on 1000 simulations



Once again, Figures 9 and 10 show the poor performance of the deconvolution method. In the average SSE plot for all the stimulus sequences, the SSE of the deconvolved HRF is much larger than those of the other extracted HRF's. The LS-F and LS-T methods have curves that overlap on many of the SSE and correlation plots. The only differences occur for stimulus sequence 1, where the SSE for LS-T is much less than for LS-F, and stimulus sequence 3, where the SSE for LS-F is less than for LS-T for noise standard deviation greater than 2 or 3. For most of the simulations, the HRF from the Wiener filter has lower SSE than the deconvolved HRF, but greater than that of the LS-T and LS-F HRF's. This relationship is similar with respect to correlation with the true HRF, better than deconvolution and worse than LS-T and LS-F. The Wiener filter gives the best extraction in these simulations for stimulus sequence 3 with regard to SSE and correlation, when the noise standard deviation is greater than 2.

5.3 Performance of the Fit of Two-Gamma-Difference Model

Figure 11 plots the SSE against the standard deviation of the noise, where SSE is calculated as the sum of squared deviations of the fitted two-gamma-difference HRF from the true HRF. Figure 11 is similar to Figure 9, but allows comparisons of the fitted models from the extraction methods with the fitted model using the convolved fit. Figure 12 plots the average correlation of the fitted HRF with the true HRF. The relationship between Figures 10 and 12 is the same as the relationship between Figures 9 and 11.

The most important thing to notice in Figures 11 and 12 is that the convolved fit consistently has the lowest SSE and the highest correlation in relation to the true HRF, with the exception of SSE for high noise variance in stimulus sequence 1. However, this is a little deceiving since the correlation is much higher for the convolved method than for any of the others. For the extraction methods, the quality of the two-gamma-difference model fit from the LS-T, LS-F, deconvolution, and Wiener filter methods are generally similar to the quality of their extracted (unfitted) HRF's. Most notably, the model fit to the LS-F and LS-T extractions have very similar SSE from and correlation with the true HRF, which are better than the others. The only exception to this is the Wiener filter in stimulus sequence 3, where it has better SSE and correlation than all of the other extraction methods. In practice, the performance of the Wiener filter extraction may not be better than the other methods since it depends on the accuracy of the estimate of the noise variance (see Section 2.2).

Figure 11: Average SSE of Fitted HRF from True HRF, based on 1000 simulations

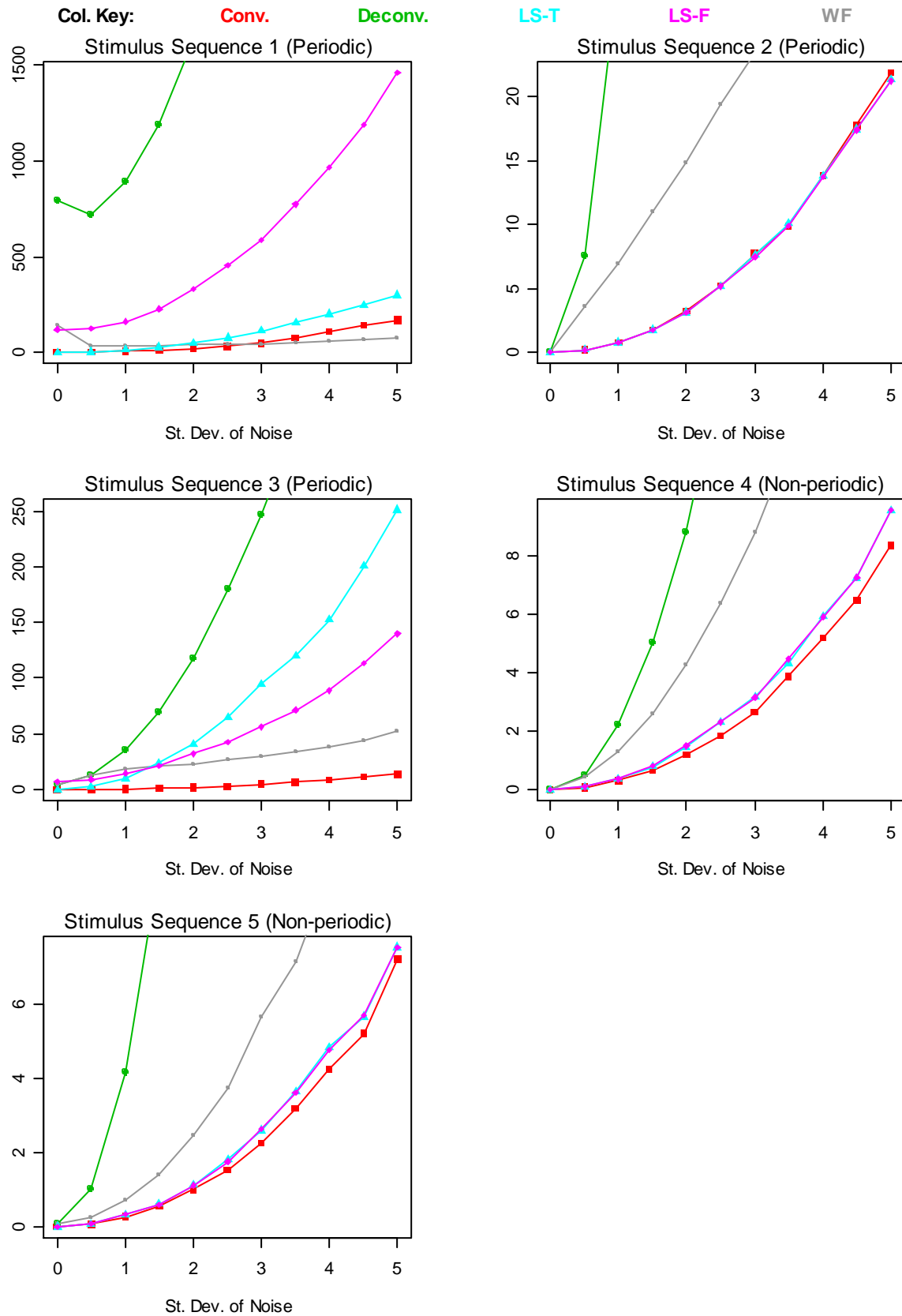


Figure 12: Average Correlation of Fitted and True HRF, based on 1000 simulations

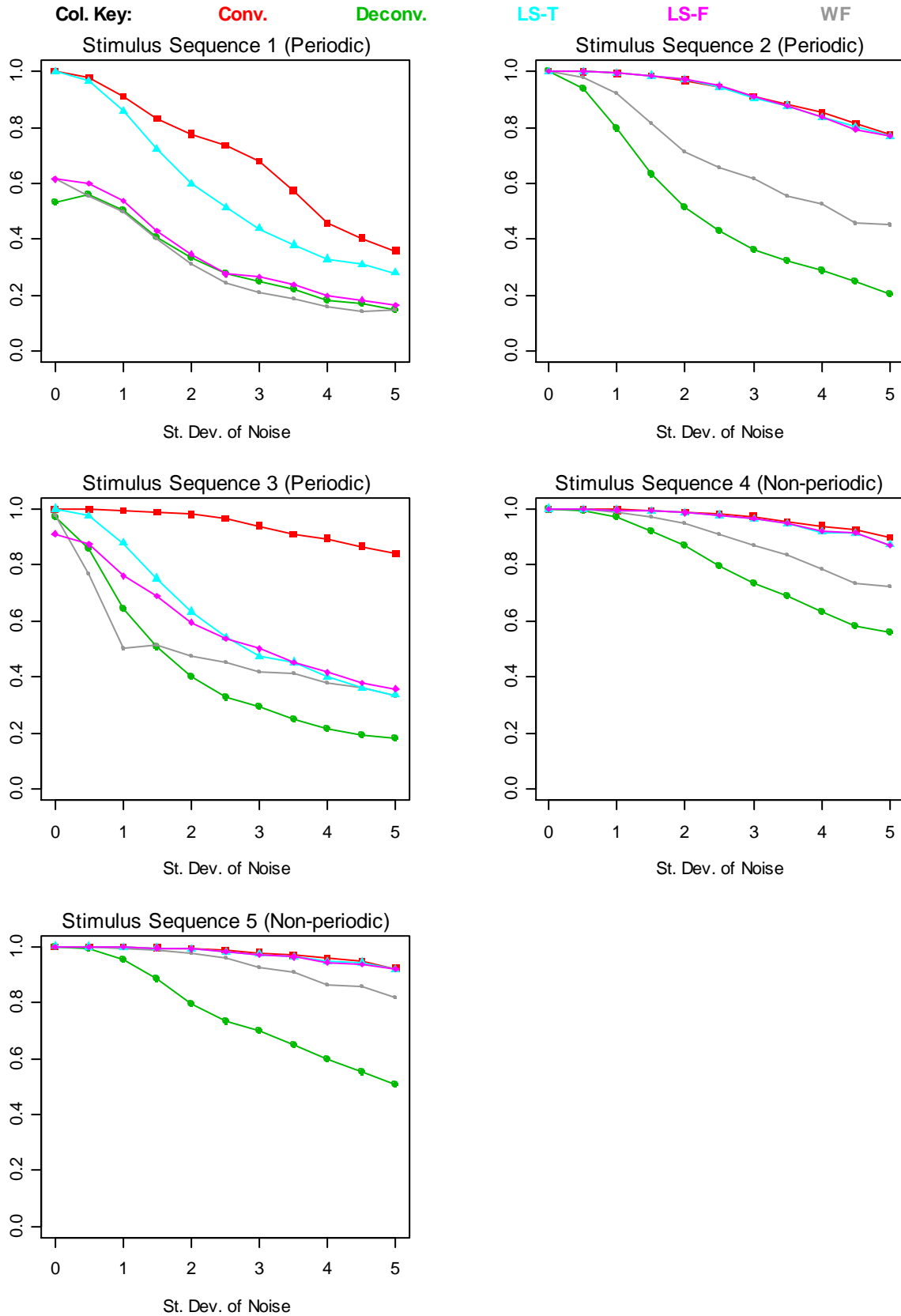


Table 1 summarizes the performance of the parameter estimates in this simulation study. For each parameter, the median parameter estimate was compared to the parameter from which the data were simulated to obtain its relative error (RE). The average SSE and correlation of the fitted HRF from the true HRF are given as well, corresponding to the values graphed in Figures 11 and 12. The relative error of the parameter estimates can provide useful information about the physiological conclusions from the fitting method. For example, if it is important to estimate the time of the HRF peak or valley, the relative error of d_1 and d_2 would be of particular interest. While the parameter estimates represent an important aspect of the quality of the model fit, notice that the correlation with the true HRF can be very high and the SSE from the true HRF can be very low even when the parameter estimates have large relative errors. For this reason, the correlation and SSE should also be an important evaluator of the fitted two-gamma-difference models.

Table 1: Numerical Summary of Parameter Estimates from 1000 Simulations

Fitting Method	Stim Seq	St. Dev. Of Noise	RE of Median a1	RE of Median a2	RE of Median d1	RE of Median d2	RE of Median c1	RE of Median c2	Average SSE from True HRF	Average Corr with True HRF
LS-F	stim 1	3.5	73.99%	185.64%	27.34%	46.11%	589.43%	1055.79%	772.35	0.240
LS-T	stim 1	3.5	64.46%	109.99%	14.76%	-7.24%	751.28%	946.58%	154.40	0.380
Deconv	stim 1	3.5	31.22%	190.16%	41.71%	50.45%	1140.36%	2486.49%	3732.52	0.220
WF	stim 1	3.5	8.97%	-9.79%	18.07%	-25.05%	355.49%	841.40%	51.56	0.189
Conv	stim 1	3.5	15.71%	-36.61%	13.73%	-15.83%	220.21%	320.93%	74.69	0.574
LS-F	stim 2	3.5	-11.56%	-29.50%	5.84%	-5.80%	41.64%	100.50%	9.91	0.876
LS-T	stim 2	3.5	-11.72%	-31.57%	5.76%	-5.95%	39.54%	100.35%	10.04	0.878
Deconv	stim 2	3.5	28.93%	0.77%	8.34%	-8.98%	438.89%	868.87%	346.16	0.325
WF	stim 2	3.5	-1.22%	-19.51%	1.91%	-5.00%	129.92%	181.48%	28.06	0.556
Conv	stim 2	3.5	-15.38%	-34.90%	8.24%	-5.23%	42.71%	105.80%	9.87	0.883
LS-F	stim 3	3.5	28.37%	36.74%	12.87%	-10.01%	462.88%	787.89%	71.38	0.451
LS-T	stim 3	3.5	39.66%	30.95%	10.41%	-12.05%	570.89%	723.86%	120.19	0.453
Deconv	stim 3	3.5	48.03%	49.65%	18.82%	-14.21%	1604.22%	3121.01%	327.00	0.248
WF	stim 3	3.5	-14.94%	-10.75%	-12.47%	-35.10%	206.39%	310.52%	34.11	0.412
Conv	stim 3	3.5	-7.64%	-18.30%	3.73%	-5.50%	27.13%	69.41%	6.72	0.909
LS-F	stim 4	3.5	-12.61%	-24.11%	4.17%	-4.16%	15.75%	45.14%	4.46	0.949
LS-T	stim 4	3.5	-11.83%	-23.16%	4.16%	-3.88%	15.87%	46.62%	4.32	0.948
Deconv	stim 4	3.5	26.97%	10.50%	6.52%	-4.39%	159.03%	220.62%	27.08	0.691
WF	stim 4	3.5	-12.48%	-26.86%	5.02%	-5.51%	24.11%	77.93%	11.65	0.838
Conv	stim 4	3.5	-15.96%	-25.24%	3.49%	-4.41%	18.21%	51.44%	3.86	0.952
LS-F	stim 5	3.5	-10.05%	-35.53%	3.69%	-5.03%	20.32%	37.28%	3.60	0.962
LS-T	stim 5	3.5	-10.21%	-34.76%	3.59%	-5.01%	20.62%	37.46%	3.63	0.964
Deconv	stim 5	3.5	-28.17%	-19.63%	14.65%	-9.05%	132.76%	428.42%	48.11	0.647
WF	stim 5	3.5	-11.23%	-39.03%	3.27%	-4.41%	22.47%	61.83%	7.13	0.906
Conv	stim 5	3.5	-15.30%	-37.24%	4.80%	-5.85%	22.69%	44.31%	3.19	0.969

VI. Conclusions

When a nonparametric estimation of the HRF is required, the LS-T and LS-F extractions

are the best choices in most cases based on these simulations. The Wiener filter, however, appears to be a better choice for stimulus patterns such the one in stimulus sequence 3. This will only be true when a good estimate of the noise variance is available. When one is not available, the LS-F extraction should be used for those kinds of highly periodic, highly clustered stimulus sequences. There is no situation in which the deconvolved HRF is better than any other extracted HRF. If one extraction method had to be recommended, the LS-T extracted HRF consistently produces a fairly good representation of the HRF while being very computationally efficient.

When a two-gamma-difference model fit of the HRF is desired, the convolved method appears to provide the best method for the stimulus sequences included in this study. Since the reliability of the results of this study depends on the reliability as the two-gamma-difference model for the HRF, further simulation studies should investigate the quality of these methods for fMRI signals simulated from alternative models. These models could include a pre-undershoot, a correlated error structure, and accommodation for the possibility of a non-constant HRF, especially within one experiment. Furthermore, these simulations do not take into account the effect of the removal of trends in the fMRI signal.

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Appendix: R functions for Extraction of the HRF

The following functions written in R were used in the simulation to extract the first 32 seconds of the HRF. `data` refers to the raw fMRI time series. `stim` refers to the stimulus sequence and is the same length as `data` with ones at the stimuli and zeroes elsewhere. `dhrf` is the duration of one HRF in time points, i.e. 32 seconds of time points. `n` is the number of time points in the data and stimulus. Each function returns the HRF, truncated at value of `dhrf`.

Deconvolution:

```
deconvolution <- function(data,stim,dhrf,n,cutoff = 6) {
  # cutoff is a parameter that determines the cutoff point for handling Fourier
  # coefficients that are equal to or close to zero. Lower values result in a smoother
  # extracted HRF.
  fftdata <- fft(data)
  fftstim <- fft(stim)
  stim.filter <- fftstim*(abs(fftstim)>0)+1/cutoff*(abs(fftstim)==0);
  inv.filter <- 1/stim.filter
  inv.filter <- inv.filter*(abs(fftstim)*cutoff > 1) +
  cutoff*abs(stim.filter)*inv.filter*(abs(stim.filter)*cutoff <= 1)
  return(Re(fft(fftdata*inv.filter,inverse=T)/n)[1:dhrf])
}
```

Wiener Filter Extraction:

```
wiener.filter <- function(data,stim,dhrf,n,est.noise,cutoff = 3) {
  # cutoff is the same parameter used in the deconvolution. est.noise is a vector
  # of observed noise used to estimate the noise variance.
  fftdata <- fft(data)
  Ys <- Mod(fftdata)^2/n
  fftstim <- fft(stim)
  Ns <- var(est.noise)
  NSR <- Ns/Ys
  S.filter <- fftstim*(abs(fftstim)>0)+1/cutoff*(abs(fftstim)==0);
  Syy <- Mod(S.filter)^2
  S.inv.filter <- 1/S.filter
  S.inv.filter <- S.inv.filter*(abs(fftstim)*cutoff > 1) +
  cutoff*abs(S.filter)*S.inv.filter*(abs(S.filter)*cutoff <= 1)
  W.filter <- S.inv.filter*Syy/(Syy+NSR)
  return(Re(fft(W.filter*fftdata,inverse=T)/n)[1:dhrf])
}
```

LS-F:

```
extract.freq <- function(data,stim,dhrf,n, cutoff = 3) {
  # cutoff is the same parameter used in the deconvolution and Wiener filter.
  fftstim <- fftstim*(abs(fftstim) > 1/cutoff) + 1/cutoff*(abs(fftstim) <= 1/cutoff)
  fftdata <- fft(data)
  fftstim <- fft(stim)
  obj.fn <- function(hrf,fftdata,fftstim,dhrf,n) {
    temp <- (fftdata-fftstim*fft(c(hrf,rep(0,n-dhrf))))
    return(sum(temp*Conj(temp)))
  }
  start <- rep(0,dhrf)
  hrf <- optim(par=start,obj.fn,method="L-BFGS-B",
    fftdata=fftdata,fftstim=fftstim,dhrf=dhrf,n=n)
  return(hrf$par)
}
```

LS-T:

```
extract.time <- function(data,stim,dhrf,n) {
  # X is the design matrix for this linear regression problem, with a parameter for
  # each time point (dhrf of them) in the extracted HRF.
  X <- matrix(rep(0,n*dhrf),n,dhrf)
  for (i in 1:n) X[i,1:min(i,dhrf)] <- stim[i:max(i-dhrf+1,1)]
  return(solve(t(X) %*% X) %*% t(X) %*% data)
}
```