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Structural adaptive smoothing for single-subject analysis in SPM: the *aws4SPM*-toolbox

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Abstract

There exists a variety of software tools for analyzing functional Magnetic Resonance Imaging data. A very popular one is the freely available SPM package by the Functional Imaging Laboratory at the Wellcome Department of Imaging Neuroscience. In order to enhance the signal-to-noise ratio it provides the possibility to smooth the data in a pre-processing step by a Gaussian filter. However, this comes at the cost of reducing the effective resolution. In a series of recent papers it has been shown, that using a structural adaptive smoothing algorithm based on the Propagation-Separation method allows for enhanced signal detection while preserving the shape and spatial extent of the activation areas. Here, we describe our implementation of this algorithm as a toolbox for SPM.

1 Theoretical background

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive tool for studying the functionality of the brain, searching for brain activation, and localizing cognitive functions. In the past decades, it has become increasingly important in neurosciences as well as for clinical applications such as presurgical planning. However, activation in brain is not subject to direct measurement. Second level characteristics are therefore used as indication of brain activity. One of them is the change in blood oxygenation (BOLD response) [6, 7] connected with some task the subject is to perform during the scan. A higher oxygenation level is associated with increased neuronal activity necessary to solve the task.

In a typical block-design fMRI experiment the subject has to perform one or several tasks alternated by some period of rest. In the following we review the analysis of such fMRI data using a linear model for the expected BOLD response and show, how to include structural adaptive smoothing into this analysis. The original work has been published in [13]. In a series of papers the use of this smoothing algorithm in several applications [10, 12, 14] has been demonstrated.

1.1 fMRI analysis using linear modeling

In fMRI, the BOLD effect can be used as a natural contrast employing the fact that voxels with increased neuronal activity are characterized by a higher oxygenation level [6, 7]. The expected BOLD response can be modeled by a convolution of the task indicator function with the hemodynamic response function. This function accounts for the fact that blood oxygenation is subject to some delay and shows a more complex structure than a simple indicator function [3]. For the rest of this paper we simply assume that we are *able* to model the expected BOLD-response as the specific model is not relevant for all considerations henceforth.

Here, we adopt the common view [2, 15, 18], of a linear model

$$Y_i = X\beta_i + \varepsilon_i, \tag{1}$$

for the time series $Y_i = (Y_{it})_{t=1\ldots T}$ at each voxel i after reconstruction of the raw data, where X denotes the design matrix. The first q columns of X contain the expected BOLD response for the

q different stimuli evaluated at scan acquisition times. The other $p-q$ columns may account for a slowly varying drift and possible other effects. The error vector $\varepsilon_i = (\varepsilon_{it})_{t=1\ldots T}$ is assumed to have zero expectation and is generally correlated in time t. In order to assess the variability of the estimates of β_i correctly we have to take the correlation structure of the error vector ε_i into account. An AR(1) model at each voxel i seems to be sufficient for commonly used MRI scanners [17]. After determing the correlation coefficients at each i, prewhitening transforms the model (1) into a corresponding one with approximately independent errors. We therefore henceforth assume $\operatorname{Var}\varepsilon_i = \sigma_i^2 I_T$ in (1) with the unit matrix I_T of size $T \times T$ and $X = X_i$.

Under these assumptions we obtain least squares estimates $\widehat{\beta}_i$ at each voxel i from model (1) as

$$\widehat{\beta}_i = ({X_i}^T X_i)^{-1} {X_i}^T Y_i. \tag{2}$$

The error variance σ_i^2 is estimated from the residuals $r_i = (r_{it})_{t=1\ldots T}$ of the linear model (1) as $\widehat{\sigma}_i^2 = \sum_{t=1}^T r_{it}^2/(T-p)$ leading to estimated $p \times p$ covariance matrices

$$\operatorname{Var}\widehat{\beta}_i = \widehat{\sigma_i}^2 ({X_i}^T X_i)^{-1}. \tag{3}$$

Let c be a vector of contrasts that defines the effect of interest. The estimated effects $\widehat{\gamma}_i = c^T\widehat{\beta}_i$ and their estimated standard deviations $\widehat{s}_i = \sqrt{c^T \operatorname{Var}\widehat{\beta}_i c}$ are three dimensional arrays $\widehat{\Gamma}$ and $\widehat{S}$. The voxelwise quotient $\theta_i = \widehat{\gamma}_i/\widehat{s}_i$ of both arrays forms a statistical parametric map (SPM) Θ. This map is approximately a random t-field with $T-p$ degrees of freedom, see [16]. All these arrays carry a correlation structure induced by the spatial correlation in the fMRI data. This leads effectively to a lower number of degrees of freedom for Θ, see [17].

Signal detection may be based on the SPM Θ. We consider a voxel i as activated if the corresponding value θ_i exceeds a critical value or threshold. The definition of the threshold involves a severe multiple test problem. Voxelwise thresholds based on a t-distribution for θ_i with a corresponding number of degrees of freedom lead to a large number of false positive activations due to the large number of voxels in the data cube. On the other hand the application of the Bonferroni correction does not account for the spatial correlation structure of the data. Random Field Theory [1] setting a family-wise error (FWE) can therefore be used to correct the thresholds for the number of independent tests in the data [16]. However, due to the low signal-to-noise ratio, this may fail to detect many of the activations: The high noise level σ_i may lead to values θ_i below the threshold, although there is activation at voxel i. In situations where activations have a spatial extent, spatial smoothing and thus reducing $\widehat{\sigma}_i$ has the potential to improve both overall sensitivity and specificity of signal detection.

1.2 Smoothing functional MRI data

The application of a Gaussian filter to the three dimensional images of the fMRI scan as implemented in SPM [4] has mainly two effects. First, if the activation has a spatial extent adjacent voxel will contain similar time courses and thus the averaging lowers the noise level σ_i while conserving the signal. Second, it increases the smoothness of the random field Θ and thus lowers

the number of independent tests as well as the corresponding global thresholds. However, with Gaussian smoothing we can achieve a reduction in the signal-to-noise ratio at the cost of a possible bias at the border of the activated regions only. This leads to an increased power of the tests and therefore more sensitivity and specificity of signal detection in all voxel except in a neighborhood of the border of the region. The size of this neighborhood depends on the amount of smoothing that is applied. In this neighborhood specificity of signal detection may decrease. The optimal amount of smoothing depends on both signal strength and spatial extent, see e.g. [15].

In [8] the basic principles of a novel type of structural adaptive smoothing procedures have been developed. [13] designed an algorithm for structural adaptive smoothing fMRI data based on the Propagation Separation approach discussed there. The algorithm is shortly reviewed in the next subsection. The idea behind structural adaptive smoothing is to use information on the structures of interest in the smoothing algorithm for locally modeling the data. If, for example, an anatomical image is disturbed by noise, the interesting structures may be the different tissues, which are characterized by a certain grey level value. Thus, locally the data can be described by a constant. This information can be used in our structural adaptive smoothing algorithm, which preserves shape and border of the interesting structures. For fMRI, the structures of interest can not be found in a single three dimensional image of the time series, rather than in the value of the BOLD parameter or the estimated effect $\widehat{\gamma}_i$. We expect this parameter to differ significantly from zero in activated areas and to be consistent with zero elsewhere. [13] therefore suggested to apply the structural adaptive smoothing to $\widehat{\gamma}_i$ after estimating the parameters from the linear model.

Spatial smoothing is usually applied to the original images in the fMRI time series before estimating the parameters β_i in the linear model. Except for effects from prewhitening this order is arbitrary for parameter estimation. The temporal and spatial smoothing can be interchanged if the temporal correlations are spatially homogeneous. For structural adaptive smoothing the order of both steps is important. The quality of adaptation heavily depends on the signal to noise ratio present in the data. Parameter estimation in the linear model serves as a variance and dimension reduction step prior to spatial smoothing and therefore allows for a much better adaptation. The use of the variance estimates in the algorithm uses much more information on the SPM, than simple Gaussian filtering.

1.3 Structural adaptive smoothing fMRI data

In this subsection we shortly review the structural adaptive smoothing algorithm for the parameter maps $\widehat{\Gamma}$ as proposed in [13].

Let us assume that for each voxel with coordinates $i = (i_x, i_y, i_z)$ the true parameter γ_i can be well approximated by a constant within a local vicinity $\mathcal{U}(i)$ of voxel i. This serves as our structural assumption and represents the fact, that activation is usually spatially extended and that the BOLD parameter in adjacent voxels is approximately equal. This is especially true for the non-activated voxels, where the BOLD parameter is expected to be consistent with zero.

In order to efficiently estimate the parameter γ_i from the local neighborhood we want to describe

a local model, that is, to assign weights $W_i = \{w_{i1}, \ldots, w_{in}\}$. If we knew the neighborhood $\mathcal{U}(i)$, we would define local weights as $w_{ij} = I_{j \in \mathcal{U}(i)}$ with the indicator funtion I and use the weighted least squares estimate

$$\sum_j \widetilde{w}_{ij} \widetilde{\gamma}_j / \sum_j \widetilde{w}_{ij} \quad \text{with} \quad \widetilde{w}_{ij} = w_{ij}/s_j^2 \tag{4}$$

as an estimate of γ_i. On the other hand, if we had good estimates of γ_j, we could use this information to infer on the set $\mathcal{U}(i)$ by testing the hypothesis

$$H : \gamma_j = \gamma_i. \tag{5}$$

A weight w_{ij} can be specified based on the value of a test statistic T_{ij}, assigning zero weights if γ_j and γ_i are significantly different. This provides us with a set of weights W_i that determines a local model in voxel i. These weights can then be used to obtain new estimates of the parameter function γ in each voxel i by (4).

We utilize both steps, estimation of parameters and testing homogeneity, in an iterative procedure. First we define a geometric sequence $(h^{(k)})_{k=0,\ldots k^\star}$ of increasing bandwidths with $h^{(0)} = 1$. Using the ratio $r_x, r_y, r_z = v_x, v_y, v_z / min(v_x, v_y, v_z)$ of the voxel extensions v_x, v_y, v_z, which may be anisotropic, in the three coordinate directions to its smallest value, we define the distance between two voxels i and j:

$$\Delta(i,j) = \sqrt{(i_x - j_x)^2/r_x^2 + (i_y - j_y)^2/r_y^2 + (i_z - j_z)^2/r_z^2}$$

We start with a very local model in each voxel i given by weights

$$\widetilde{w}_{ij}^{(0)} = K_{\text{loc}}(\Delta(i,j)/h^{(0)})/s_j^2. \tag{6}$$

K_{loc} is a non-increasing kernel with compact support on $[0,1]$. Initial estimates $\widehat{\gamma}_i^{(0)}$ are then generated using (4).

In the kth iteration new weights are generated as

$$\widetilde{w}_{ij}^{(k)} \quad = \quad K_{\text{loc}}(\Delta(i,j)/h^{(k)}) K_{\text{st}}(\boldsymbol{\zeta}_{ij}^{(k)})/s_j^2 \quad \text{with} \quad \boldsymbol{\zeta}_{ij}^{(k)} = T_{ij}^{(k)}/\lambda \tag{7}$$

and a non-increasing kernel K_{st} with compact support on $[0,1]$. The term

$$T_{ij}^{(k)} = N_i^{(k-1)} (\widehat{\gamma}_i^{(k-1)} - \widehat{\gamma}_j^{(k-1)})^2$$

with $N_i^{(k-1)} = \sum_j \widetilde{w}_{ij}^{(k-1)}$ is used as a test statistic for the homogeneity hypotheses (5) and λ is the main parameter in our approach, see [13, 8].

Then we recompute the estimates employing the just defined weights as

$$\widehat{\gamma}_i^{(k)} = \frac{1}{N_i^{(k)}} \sum_j \widetilde{w}_{ij}^{(k)} \widehat{\gamma}_j \tag{8}$$

where $N_i^{(k)} = \sum_j \widetilde{w}_{ij}^{(k)}$.

The resulting procedure is essentially a multiscale procedure. In each iteration we allow for a different amount of smoothing by increasing the bandwidth $h^{(k)}$. The resulting weighting scheme

excludes observations in voxel j from being used in estimating at voxel i as soon as they are detected to have significantly different expectations in one of the iteration steps. The weighting scheme ensures that, with a high probability, such decisions are kept within the following iterations. We refer to [8] for detailed properties of the weighting scheme.

Without spatial correlation $\widehat{\gamma}_i^{(k)}$ has the variance

$$V_i^{(k)} = Q_i^{(k)}/(N_i^{(k)})^2 \leq 1/N_i^{(k)} \quad \text{with} \quad Q_i^{(k)} = \sum_j (\widetilde{w}_{ij}^{(k)})^2 \widetilde{s}_j^2, \tag{9}$$

that is, the term $1/N_i^{(k)}$ approximately reflects the variability of $\widehat{\gamma}_i^{(k)}$. Spatial correlation in the data leads to incorrect assignment of the parameter variance and thus possible incorrect adaptation, see [13] how to correct for this.

1.4 Signal detection using the smoothed statistical parametric map

Structural adaptive smoothing results in arrays $\widehat{\Gamma}^\star = (\widehat{\gamma}_i^\star)$ and $\widehat{S}^\star = (\widehat{s}_i^\star)$. If no activation is present in any voxel, i.e the hypothesis H: $\gamma_i = 0$ holds for all i, choosing the smoothing parameter λ by the propagation condition [13, 8] ensures the properties of $\widehat{\Gamma}^\star$ and $\widehat{S}^\star$ to approximately coincide with properties of the corresponding arrays obtained by nonadaptive smoothing employing the kernel K_{loc} with bandwidth $h^{(k^*)}$.

Furthermore, through smoothing the variance of the parameter estimates has been reduced. In spatially extended activated areas this leads to larger values for the t-statistics, which eventually may be larger than the threshold and thus the correspondiong voxels also be detected as activ. On the other hand, the smoothness of the random field has been increased, which weakens the multiple test problem due to the reduction of number of independent tests. Interchanging the order of smoothing and linear modeling leads to an increased number of degrees of freedom for the t-field making it more Gaussian [13]. Inference can now be based on the smoothed map $\Theta^\star$.

2 The toolbox *aws4SPM*

In this section we describe in detail our implementation of the structural adaptive smoothing method described above as a toolbox in SPM [4] and show examples of its use. This document refers to version 0.4.0 of the toolbox. An implementation [9, 10] of this algorithm in R [11] which has more features is under constant development.

> **NOTE!** This toolbox comes with absolutely **no warranty**! It is **not** intended for clinical use, but for evaluation purpose only.

Although we carefully tested our implementation, the absence of bugs cannot be guaranteed. Since the toolbox is under development, some theoretically required corrections and calculations may not yet be fully implemented or described in this document. For more information see `http://www.wias-berlin.de/software/aws4SPM`.

2.1 Downloading and installing the toolbox

The toolbox *aws4SPM* requires *Matlab* [5] and *SPM* [4] to be installed on your computer. The toolbox can be downloaded at `http://www.wias-berlin.de/software/aws4SPM`. After downloading the toolbox archive, extract the files into your *SPM* working directory. The archive contains a C-file "smAd.c" which has to be compiled before using. In order to do this launch *Matlab* in your working directory. Compile the source file by entering the command

```
mex smAd.c
```

which finishes the installation. You can now start *SPM* and use the toolbox.

2.2 Step-by-step

This section goes step-by-step through an example analysis. Note, that currently the toolbox can only handle single-subject studies using t-contrasts. The extension for multi-subject studies is still under development and will possibly be included in a future version of the toolbox.

For our example we choose the FIAC (functional image analysis contest) data set. The original fMRI experiment investigated the sensitivity of cortical regions to auditory sentence comprehension as well as the voice of the speaker. The participants passively listened to auditory sentences in four conditions with different and repeated sentences and speakers. The experiment was run four times for each subject. In the blocked design, each 20s block (6 sentences, one every 3333 ms, with variable silence between sentences due to variation of sentence length) of sentences was separated by a 9 sec block of silent rest. For our example we used run 1 from *subject*0.

After downloading and installing the toolbox *aws4SPM* in your working directory start *Matlab* and *SPM*. Define the fMRI design with the four conditions and the *unsmoothed (!)* data as usual

by selecting the "fMRI time-series"-button. Now estimate the parameters of the defined linear model pressing the "Estimate"-button. Select the just created "SPM.mat" file and press "done" and thereafter "continue". If you want to use the adaptive smoothing procedure, confirm that you want to smooth additionally.

It is important to note, that you have to define a t-contrast before smoothing. The reason is, that our adaptive smoothing procedure operates on the volume of estimated parameters. This is in contrast to the common procedure of smoothing the volumes at every time step separately *before* estimating the parameters of the linear model (see section 1 and [13] for details). In our example we choose the contrast vector $c^T = (1, 0, 0, 0, 0)$ just for demonstration, not for any scientific purpose.

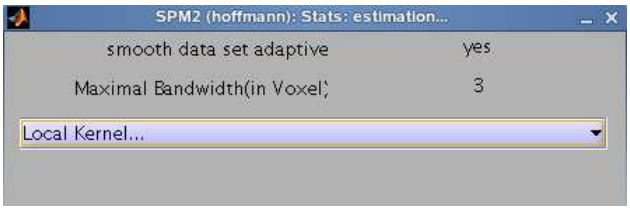


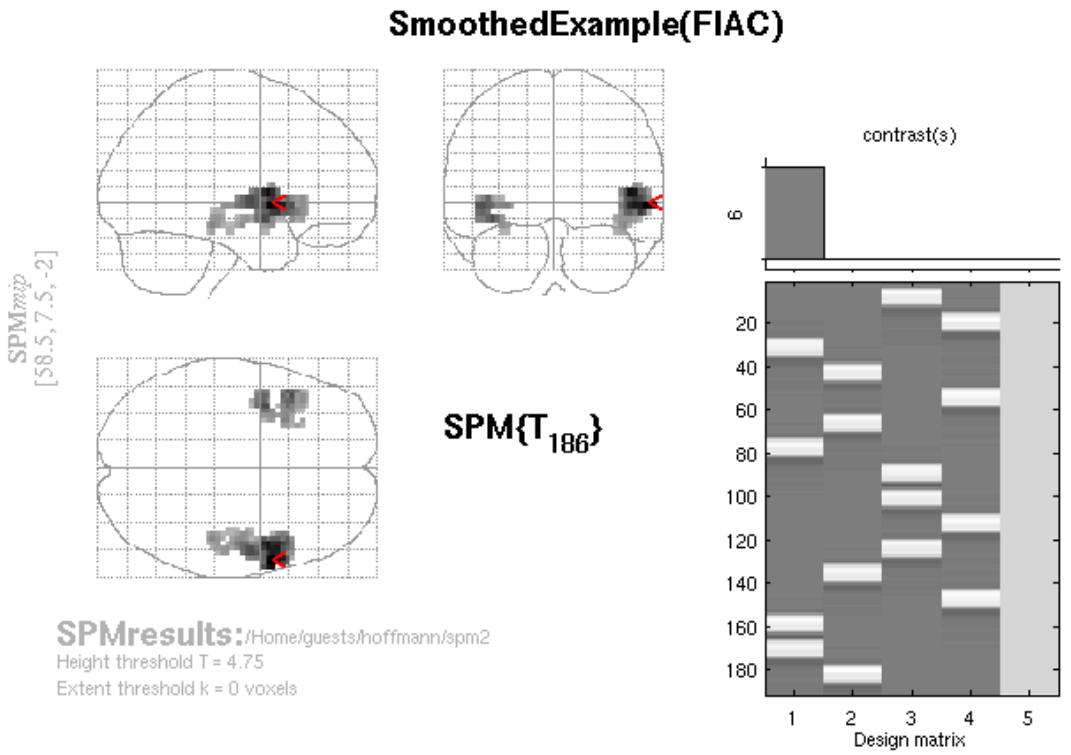
Figure 1: Extra box with the example's smoothing settings after choosing adaptive smoothing.

Adaptive smoothing requires a few parameters to choose (see Fig. 1). The most important parameter is the maximum bandwidth h_{max} for the smoothing (see section 1). It defines both the smoothness in homogenous regions of the estimated parameter contrast $\gamma = c^T\beta$ from the linear model (1) and the complexity of the algorithm. Choosing higher bandwiths increases the computation time. In fact, the time is approximately propertional to the third power of h_{max}. Since the smoothing naturally adapts to the structures in the smoothed volume, oversmoothing of the borders of activation areas is not expected. However, the notion of border of activation area for the BOLD-response may not be well defined. A reasonable choice of h_{max} is therefore a value in the order of the largest expected activation areas. Note that h_{max} is given in voxel units not in mm and refers to the support interval of the kernel function. If you choose a Gaussian kernel and want to achieve a specific FWHM bandwidth (in voxels), use $h_{max} = 0.43FWHM$.

The second item to be choosen is the location kernel K_{loc} which has only minor influence on the smoothing result. Thus it is reasonable to use a computationally simple kernel function rather than the Gaussian kernel. For our example, we used $h_{max} = 3.0$, $K_{\text{loc}} = Epanechnikov$.

The smoothing will take about two minutes on common computer hardware. To view the results click "Results". Select the "SPM.mat" and your earlier created contrast and choose the required settings. In our example we used no masking with other contrasts and a p-value of 0.05 for the family-wise-error (FWE) and get the result in Fig. 2. Two main clusters can be seen, one containing 232 voxels, the second 109 voxels, and with maximal t-values of about 7-10. The computed threshold, with a (FWE) of 0.05, is 4.75.

Figure 3 shows the signal detection in several slices of the unsmoothed data (left), of the smoothed data using non-adaptive smoothing (center) (Gaussian Kernel, bandwidth = 3.0) and of adaptively smoothed data (right). For this figure, we used the Matlab function *display_slices*, which can be downloaded at `http://imaging.mrc-cbu.cam.ac.uk/imaging/DisplaySlices`. Smoothing the data increases the signal-to-noise and mainly two activation areas show up. The main difference between the center and the right part of the figure is the apparent blurring for the non-adaptive



Statistics: *p-values adjusted for search volume*

set-level		cluster-level			voxel-level					x,y,z {mm}		
p	c	p corrected	k E	p uncorrected	p FWE-corr	p FDR-corr	T	(Z=)	p uncorrected			
0.001	**3**	**0.000**	**232**	**0.000**	**0.000**	**0.000**	**10.25**	**Inf**	**0.000**	**58**	**8**	**-2**
					0.000	0.000	9.62	Inf	0.000	46	4	6
					0.000	0.000	9.39	Inf	0.000	50	10	-2
		0.000	**36**	**0.000**	**0.000**	**0.000**	**7.86**	**7.29**	**0.000**	**-38**	**2**	**-10**
		0.000	**73**	**0.000**	**0.000**	**0.000**	**7.78**	**7.23**	**0.000**	**-44**	**20**	**-2**
					0.000	0.000	6.46	6.13	0.000	-28	16	-2

Figure 2: Results of the fmri analysis of the FIAC data set with additional adaptive smoothing, examining the contrast $c^T = (1, 0, 0, 0, 0)$. Settings for smoothing: $h_{max} = 3.0$, $K_{\text{loc}} = Epanechnikov$.

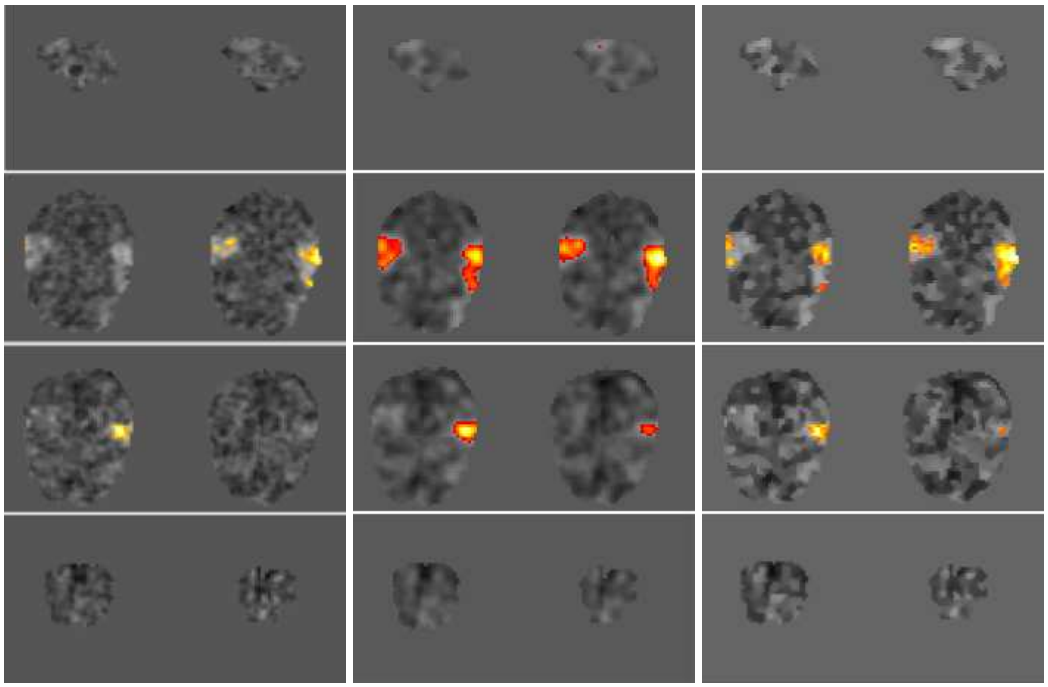


Figure 3: Signal detection in representative slices of (left) unsmoothed data, (center) smoothed data using non-adaptive smoothing and (right) adaptively smoothed data.

smoothing, whereas for structural adaptive smoothing the boundary is more detailed.

Note again, that if you want to consider another contrast for your analysis, you have to re-estimate the linear model, since per design of the current version of the toolbox, the unsmoothed parameter values are over-written.

2.3 Documentation of the implemented algorithm

The toolbox archive contains three files, namely *smAd.c*, *spm_smooth_gamma.m* and *spm_spm.m*. The latter is an updated file from the standard *SPM* installation to enter the structural adaptive smoothing procedure if requested. The other two files contain the implementation of the structural adaptive smoothing algorithm. Fig. 4 the various steps in the calculation, starting with the estimation of the parameters of the linear model.

1. *Spm_spm.m* is accessed by starting the fMRI estimation via the "Estimate" button of the main *SPM* window. Our toolbox extends the fMRI analysis by the possibility of structural adaptive smoothing a defined contrast of parameters of the linear model. The changes in this file compared to the standard *SPM* version add a new choice after estimating the parameters of the linear model and a new window for the selection of the settings for the smoothing procedure pops up (see Fig. 1). Note, that triggering the adaptive smoothing requires a contrast vector to be set. In the common *SPM* analysis this has to be chosen later, namely when viewing the results.

2. With these settings the function *spm_smooth_gamma*() is called. The function reads all estimated β-volumes and the sum of the squared residual of the linear model as 3D arrays from the files produced by *SPM* during estimation. Using the choosen contrast c a new array of estimated effect $\gamma = c^T\beta$ is calculated. This is the 3D volume that is subject to the structural adaptive smoothing procedure (see section 1 for details). The variance $Var\beta$ of these parameter estimates are calculated from the sum of squared residuals using (3). The data of both arrays is, because of dimension restrictions of *Matlab*, stored in 2D matrices (without loss), and passed to *smAd*.

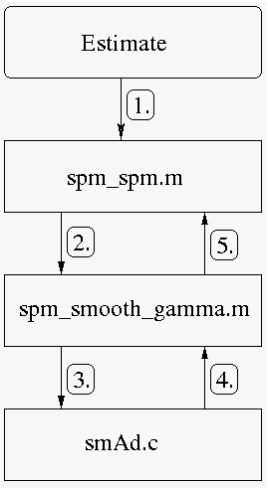


Figure 4: Sketch of the various calculation steps of the aws4SPM toolbox, see text for details.

3. In *smAd* (cf. Fig. 5) the structural adaptive smoothing is performed. The entry point in this file is, like in every *Matlab* C-file, the $mex()$ method. First of all, the input data is transformed to suiting data types. For this purpose mainly float pointers are used. With the settings declared by the user in the dialog box in Fig. 1 and additional required data (γ, $Var\beta$, see Fig. 5) $smoothAdaptive()$ is called, which forms the heart of the algorithm. After some preparation like initializing the starting weights $\omega_i^{(0)}$, see Eq. (6), the main loop of the iteration is called, see Eqs. (7) and (8). At each step k of the iteration new estimates for $\gamma_i^{(k)}$ and new weights $\omega_i^{(k)}$ at each voxel are computed using Eqs. (8) and (7). For this, $calculateGammaI()$ or $calculateGammaIGauss()$ are called, depending on the chosen kernel K_{loc}. Both sum up the weights $\omega_{ij}^{(k)}$ for each voxel i and hence calculate a new estimate for $\gamma_i^{(k)}$. To optimize the program's speed we exploit the fact that the kernel functions have compact support (for the Gaussian kernel we use a cut-off at 4 standard deviations) with no influences on the result. Also, due to that reason, we implemented the Gaussian Kernel variant for the location kernel K_{loc} in a separate function. Selecting the Gaussian kernel as location kernel, the adaptive smoothing will take more time. $CalculateGammaI(Gauss)$ calls the $kernVal()$ to calculate the kernel values. It is used to calculate the location penalty K_{loc} as well as the statistical penalty K_{st}. Several kernels like the Epachnenikov and Plateau kernel are implemented and can be selected in the user menu in Fig. 1. In the final iteration $k = k^\star$ the variances of the final estimates $\gamma_i^{(k^\star)}$ are calculated, see Eq. (9).

4. Both volumes, the smoothed parameter map and its variances, are returned from $smoothAdaptive()$ to $mex()$ after the final iteration $k^\star$. Again, both are tranformed to 2D arrays (without any information loss) and returned to *spm_smooth_gamma*().

5. Following the road in backward direction, the variances from the final iteration are used to compute new squared residuals, see Eq.(3), and saved in the file *ResMS.img*. Therefore the signal detection can now be done as usual in *SPM*, which uses the squared residuals to calculate the variances. Note: With a slight abuse of the file the new smoothed parameter map γ is saved in the file *beta_0001.img*, although there may be more than one stimulus. To continue working with the smoothed data it is therefore necessary to choose the trivial contrast $c = (1)$. Since smoothing operates on the contrast of parameters, changing the contrast of interest requires re-estimating the

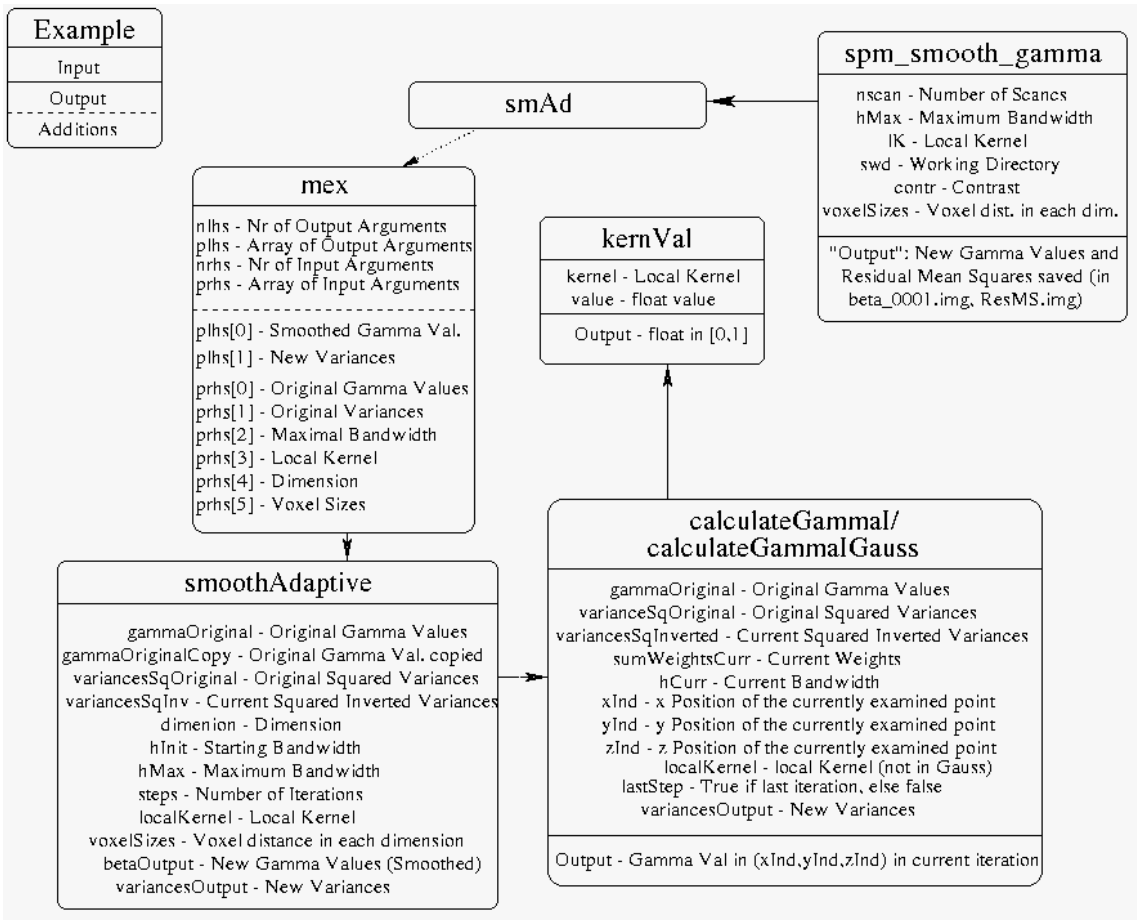


Figure 5: Interfaces of the main functions of the *aws4SPM*-toolbox, especially *smAd* and *spm_smooth_gamma*. Input and output parameters of the functions are shown together with their interpretation.

linear model!

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