

Percent Signal Change for fMRI calculations

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Quantitative scaling into percent signal change is helpful to detect and eliminate “bad” results with abnormal extreme values. While cognitive effects give signal changes on the order of 1% (and larger in the visual and auditory cortices), signal variations of over 10% may arise from motion and other artifacts in the data. Thus, a quantitative check on measured effect size can be used to screen abnormally large values likely caused by artifacts in the data.

Percent signal change for fMRI is limited in applicability because it is difficult to relate measured signals to neuronal excitations. However, percent signal change is easily defined for an fMRI block design experiment when the noise is small and the response is relatively flat (Figure 1). Our objective is to quantify the imaging pipeline starting from this collected data. This note describes the quantitative scaling laws that make the General Linear Model (GLM) estimation output from SPM consistent with this definition.

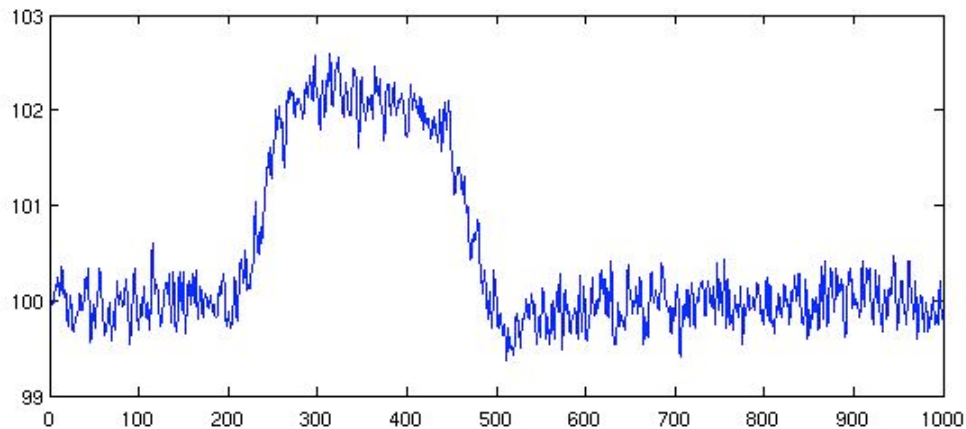


FIGURE 1: Simulated block design output showing a baseline signal of 100, and block amplitude estimated as a 2% signal change. The mean of the overall timeseries is 100.4.

The scaling method is based on the SPM approach to specifying the General Linear Model. Three scale factors are involved in percent signal change: (1) peak value in the design matrix, (2) normalization by a baseline value, and (3) the sum of the positive terms in the contrast vector [Luo and Nichols, 2003]. These factors have been incorporated into the Global Quality scores in the ArtRepair software package [Mazaika]. While this discussion is targeted for SPM and interpreting Global Quality scores, a similar tutorial is available for FSL [Mumford].

Scale Factor 1: Peak Value in the Design Matrix

Consider the GLM equation

$$y = X\beta + \varepsilon$$

where y is the time series expressed in percent signal change. If the peak of the design regressor in X were unity, then the solution β would be in percent signal change. For example, if the measured contrast in y were 2% for a block design, and the on-off regressor for the design were $X = [0\ 1\ 0\ 1\ 0\ 1\ 0\ 1]^T$, then the solution will be $\beta = 2$, so the estimated contrast is 2%. However, if X were $[0\ 2\ 0\ 2\ 0\ 2\ 0\ 2]^T$, the solution would be $\beta = 1$, which does not equal the observed change in y . Thus, the estimated percent signal change of the signal y is the calculated β from the equation multiplied by the peak value of X . Thus, the first quantitative scale factor is the *peak* of the design matrix X . The same peak analysis applies for well-spaced event related experiments, where the peak of the design regressor should be one.

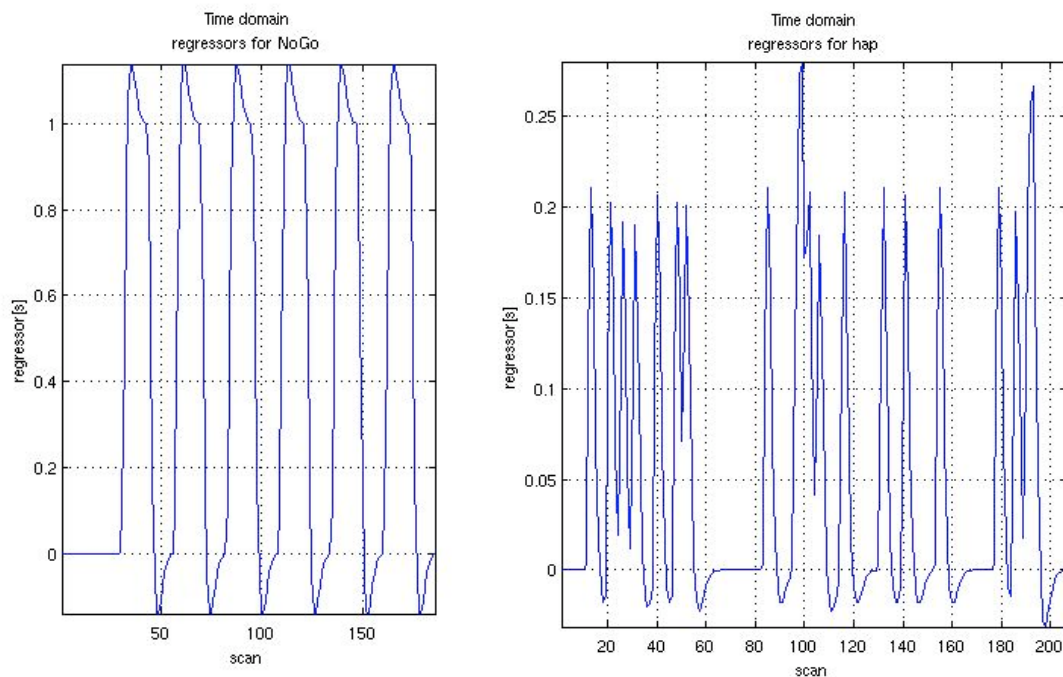


FIGURE 2: Peak of the design regressor for block experiment (left) and event related experiment (right). The display is obtained in the SPM GUI with Review Design, select Explore, select Session, select Variable, and observing the display in the upper left corner of the Graphics Window. The block events have a peak of 1.14. The peak value for an event related experiment is the peak of an isolated event, which is 0.21 in this figure.

Example: An interesting illustration is a mixed block and event design. The principle of linear superposition implies the net effect of several successive stimuli is roughly the sum of their respective individual HRF responses. In particular, this means that a block

experiment will have a larger contrast percent signal change than an event related experiment because the block will superimpose two or more individual HRFs on top of each other (see Figure 3). This simulated data could be modeled as blocks or events. If just the block were modeled with a peak of one, then $\beta = 2$, implying the block shows a contrast of 2%. If events were modeled as an HRF with a peak value of 1, and the block were modeled as a superposition of closely-spaced events, then $\beta = 1$, implying the peak of the event HRF is 1%. Note that the estimated response of the block (composed of overlapping events) is then 2% as before.

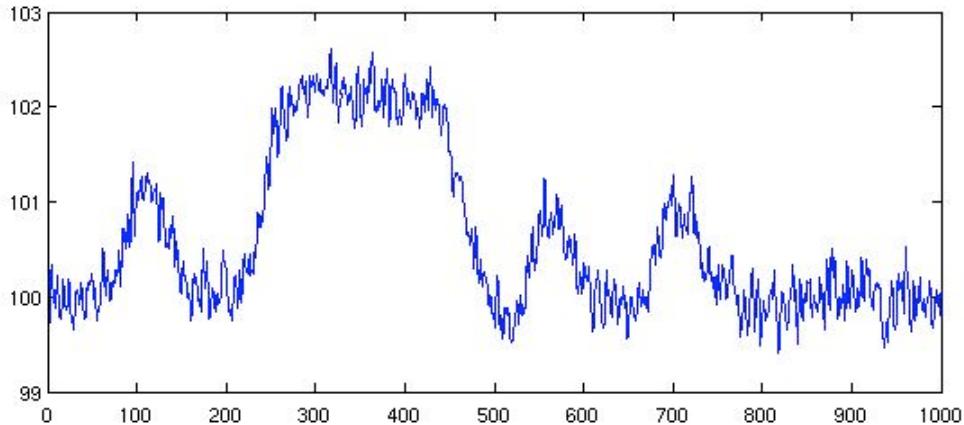


FIGURE 3: Simulated block and event design, where block is a linear superposition of closely spaced events (about 3 secs apart). When the GLM is correctly scaled, the block height is 2% whether the data is modeled as a block or as overlapping events. Mean of the timeseries is 100.6.

Scale Factor 2: Percent signal change

Percent signal change is often calculated using a baseline of the mean of the time series on a voxel. The Marsbar software will calculate a baseline from the mean signal over a small ROI of many voxels [Brett]. Instead, we will use the mean intensity over all the voxels in a brain mask as the baseline. This choice has the advantage of scaling results of all the voxels by the same conversion factor. However, it affects the percent signal change relative to a calculation that normalizes by the intensity of gray matter alone. For a brain with 35% white matter that is 15% brighter than gray matter, the net reduction on the percent signal change using the whole brain average would be about 5% relative to a baseline of only gray matter. Generally, this magnitude of difference is small relative to other errors. Similarly, the threshold used for the whole brain mask has only a small effect for reasonable range of thresholds. The whole brain mask we use is the ArtifactMask, with results that are close to using the SPM derived head mask.

Percent signal change is calculated by dividing the time series signal by the baseline (which is whole brain average in our case). In the GLM for SPM, this scaling step is equivalent to dividing the beta image by the mean beta of the constant term over the

masked brain. If beta were 1, and the mean of the constant over the brain were 100, then the estimate represents a 1% signal change. Note that Grand Mean scaling in SPM converts all values so that the mean over the brain gets closer to 100, but may not be 100, so the contrast image itself may not be in percent signal change. (The mean is often 140-180 for Lucas Center scans). We calculate the mean *bmean* to find the baseline average of the constant term over the brain.

Combining the first two scale factors gives a formula for effect size in percent signal change.

$$\beta(\%) = \beta * (peak / bmean) * 100$$

This formula is most accurate for isolated blocks or events, but can severely underestimate true effect sizes in rapid event experiments...see the discussion later.

Scale Factor 3: Contrast Sum

The subtraction paradigm is often used in fMRI to find the difference between two conditions. These experiments don't measure the "absolute" percent signal change of a signal from rest, but rather the difference of two signals, or relative percent signal change. Contrasts in the GLM are comparisons of one effect size to another. As long as each effect was estimated in percent signal change, then the difference between them is in percent signal change. However, for multiple session experiments, the same contrast could be counted multiple times. Similarly, in combined contrasts, there may be several contrasts that are added together. The contrast image is generated as the sum of images as described by the contrast vector (see Figure 4).

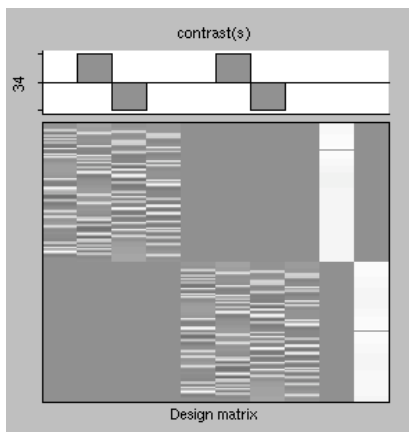


Figure 4: SPM picture of contrast vector for a two session experiment with a contrast vector of [0 1 -1 0 0 1 -1 0 0 0]. The contrast sum is two. (It is more accurate to know the coefficients used in the contrast vector rather than look at the picture. The Global Quality program will automatically find the sum from the SPM.mat file.)

In order to find the average contrast, we need to divide by the sum of the positive contrasts (there are an equal number of negative contrasts since the sum is zero). Thus, the third quantitative scale factor is the sum of positive values in the contrast vector. The contrast sum *contrastsum* depends on the particular contrast being analyzed, and must be calculated separately for each contrast. (A beta image does not need this scaling, as it is equivalent to having a contrast vector with a single 1 and all other values being zero, thus its *contrastsum* = 1.)

Thus, the complete scaling for percent signal change of contrasts is that:

$$con(\%) = (con / contrastsum) * (peak / bmean) * 100$$

where *con* is contrast image produced by SPM estimation. This formula is most accurate for isolated blocks or events, but may underestimate true effect sizes in rapid event experiments.

Rapid Event-Related Designs affect beta values

The observed effect size for beta can be markedly reduced in rapid event experiments. The previous examples had assumed the blood stream returned to a rest state between events, so that the entire contrast from peak to rest were easily visible. Rapid event related experiments decrease the estimated effect size because the continued stimuli may never let the system to return to a rest state (see Figure 5). In this simulated example, events with HRF amplitude of 1% are alternated with events with HRF amplitude 1.5% with an Inter-Stimulus Interval (ISI) of 4 seconds. The net effect is to raise the mean value of the signal to 101.25, thereby sharply reducing the estimated beta values for the events to 0% and 0.5% respectively. Note the contrast remains about 0.5%, so the contrast amplitude in percent signal change was relatively preserved in this simple linear model, even though the beta values were profoundly affected. However, other effects such as nonlinear superposition or unknown HRF shape may degrade this accuracy.

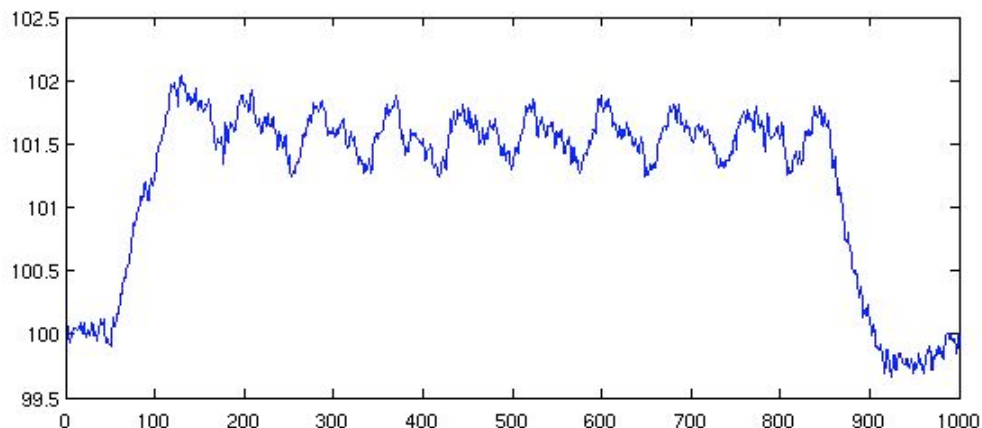


FIGURE 5: Rapid event designs reduce estimated effect size. Ten events with HRF amplitude of 1.5% are alternated with ten events of 1% amplitude. ISI was 4 seconds. Mean

of timeseries is 101.25 even though the baseline was 100. Contrast between signal types is relatively preserved.

Global Quality program finds and uses scale factors

The ArtRepair software package includes a Global Quality measure of quantitative results [Mazaika]. The Global Quality program (`>> art_summary`, in Matlab) will find the scale factors for percent signal change by reading the SPM.mat file for a single subject. The user selects a con image, and the program will find a *peak*, *bmean*, and *contrastsum* for the subject. Since there may be an error in automatically find the peak, the program prompts the user to enter a peak value, while providing the automatic value as a suggestion. The user should look at the SPM graphic displays to check the suggested peak value. Note when there are overlapping events, that the program will try to find the peak value for the isolated single events, rather than the absolute maximum peak. The output of the program will list the *peak*, *contrastsum*, and *bmean* for the subject (top, Figure 6). Different subjects in the same experiment will have the same *peak* and *contrastsum*, but *bmean* may vary (~10%) between subjects.

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/net/cibsrdata/Volumes/SPNLData03/spnlbnrc/mazaika_paul/bipolar/control_subs/00-07-
06/Results3BigafWHM7/con_0007.img,1
Statistics for Total, Inner and Outer Regions
Uses peak value 1.13, contrast sum of 1 and mean value over mask of 153
Voxels/1000    Mean      Std      RMS      Trimmean  90%ile   %Vox > 1%  AbsMax
235.1910      0.0539   0.2250   0.2313   0.0606    0.2329    0.0191     2.1133
172.7530      0.0649   0.2016   0.2118   0.0703    0.2184     0           1.7090
 62.4380      0.0233   0.2773   0.2783   0.0321    0.2781    0.0721     2.1133

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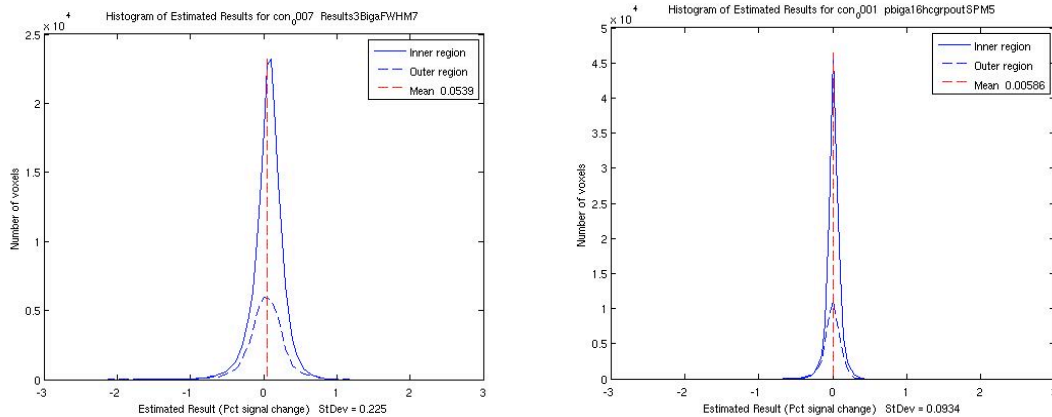


FIGURE 6: Global Quality outputs for GoNoGo block design experiments. (Top) Listing of peak value, contrast sum, and bmean. The Global Quality scores are the Mean (0.0539) and Std (.2250) over all the voxels in the brain. (Lower Left) Histogram of contrasts for the single subject shown in the top figure. (Lower Right) Histogram of contrasts for a group result of sixteen subjects. Mean is 0.00586, and Std is 0.0934.

A similar program (`>> art_groupsummary`, to be released) computes Global Quality for a group result. The user selects a beta image, or con image, and a group level SPM.mat file. The program asks for one combined scale factor $(peak/contrastsum) * (100/bmean)$ that the user can calculate after running Global Quality for the single subject results. Since

bmean varies across subjects, use a *bmean* value that is representative of the group. The output of the program will be the Global Quality results for the group result in units of percent signal change. The group result has a more narrow histogram than a single subject (lower graphs, Figure 6) because short duration experiments limit the accuracy of contrast estimates for a single subject, thereby broadening the observed distribution of contrasts.

The two programs >>art_summary and >>art_groupsummary differ in the treatment of the ResMS images to scale them into percent signal change. For the single subject case, $\sqrt{\text{ResMS}}$ is normalized into percent signal change by $(100/bmean)$, since ResMS represents fluctuations in the voxel time history. In this program, *bmean* is automatically calculated. For the group case, $\sqrt{\text{ResMS}}$ is normalized by dividing by $(\text{peak}/\text{contrastsum}) * (100/bmean)$, since ResMS represents differences in the estimated contrasts. In this program, the user enters in a *bmean* representative of the group.

Limitations of Percent Signal Change

Statistical Maps do not require percent signal change. All SPM statistics are scale-invariant so quantified results are not needed. The maps are used to spatially localize regions of the brain that show a significant effect different from zero (null hypothesis).

Quantitative results do not interpret neural excitations. The scaling does not extend back to neural excitation, because neither the BOLD effect (neural excitation to change in local dHb blood levels), or scanner effects (dHb change to recorded signal change) are well-defined. Thus, this analysis of percent signal change is only in the mathematical estimation domain, not the biology or physics domains.

The assumption of linear superposition can be violated in real data. For block experiments, the measured shape of the block response may not be particularly flat on top [Glover, 1999] due to saturation and other effects. These unusual shapes can make it tricky to define the peak or average value of even a simple block effect.

References

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