3dDeconvolve

Advanced Regression Features
Et cetera

Just in case you weren't confused enough already

Other Features - 2

http://afni.nimh.nih.gov/pub/dist/doc/misc/Decon/DeconSummer2004.html
http://afni.nimh.nih.gov/pub/dist/doc/misc/Decon/DeconSpring2007.html

- Equation solver: Program computes **condition number** for **X** matrix (measures of how sensitive regression results are to changes in **X**)
  - If the condition number is "bad" (too big), then the program will not actually proceed to compute the results
  - You can use the **-GOFORIT** option on the command line to force the program to run despite **X** matrix warnings
    - But you should strive to understand why you are getting these warnings***!!***
- Other matrix checks:
  - Duplicate stimulus filenames, duplicate regression matrix columns, all zero matrix columns


Check the screen output for **WARNING**s and **ERROR**s


  - Such messages also saved into file **3dDeconvolve.err**

Other Features - 3

- All-zero regressors *are* allowed (via **`-allzero_OK`** or **`-GOFORIT`**)
  - Will get zero weight in the solution
  - Example: task where subject makes a choice for each stimulus (e.g., male or female face?)
    - You want to analyze correct and incorrect trials as separate cases
    - What if some subject makes no mistakes? Hmmm…
      - Can keep the all-zero regressor (e.g., all **`-stim_times`** = **`*`**)
      - Input files and output datasets for error-making and perfect-performing subjects will be organized the same way

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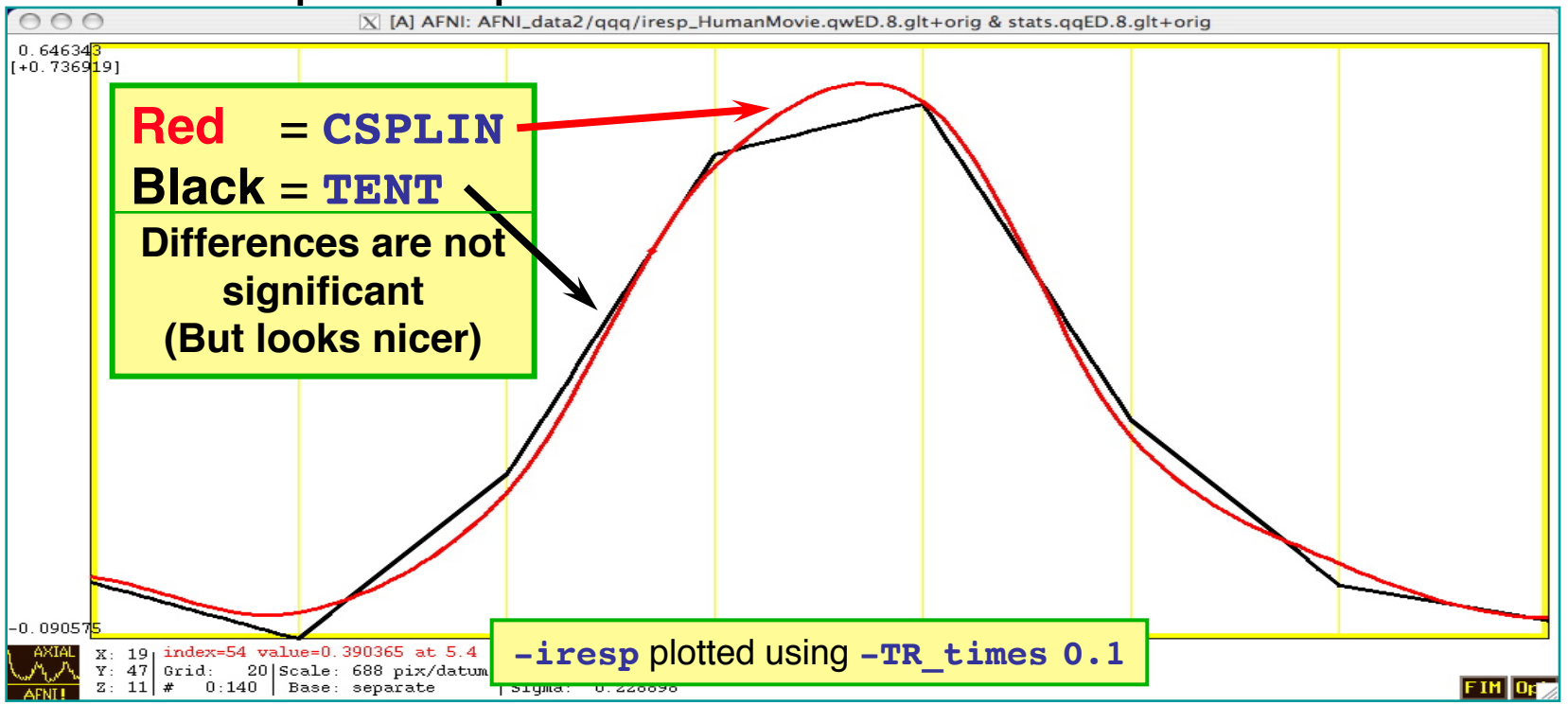
- ~~**`3dDeconvolve_f`** program can be used to compute linear regression results in single precision (7 decimal places) rather than double precision (16 places)~~
  - ~~For better speed, but with lower numerical accuracy~~
  - ~~Best to do at least one run ***both*** ways to check if results differ significantly (Equation solver *should* be safe, but …)~~

Other Features - 5

-stim_times has other basis function options for HRF model besides **BLOCK** and **TENT**

- **CSPLIN** = cubic spline, instead of **TENT** = linear spline
  - Same parameters: **(start,stop,number of regressors)**
  - A "drop in" replacement for **TENT**



- **TENTzero** & **CSPLINzero** = force start & end of HRF = 0
- **MION** = model from Leite et al. (*NeuroImage* 2002)

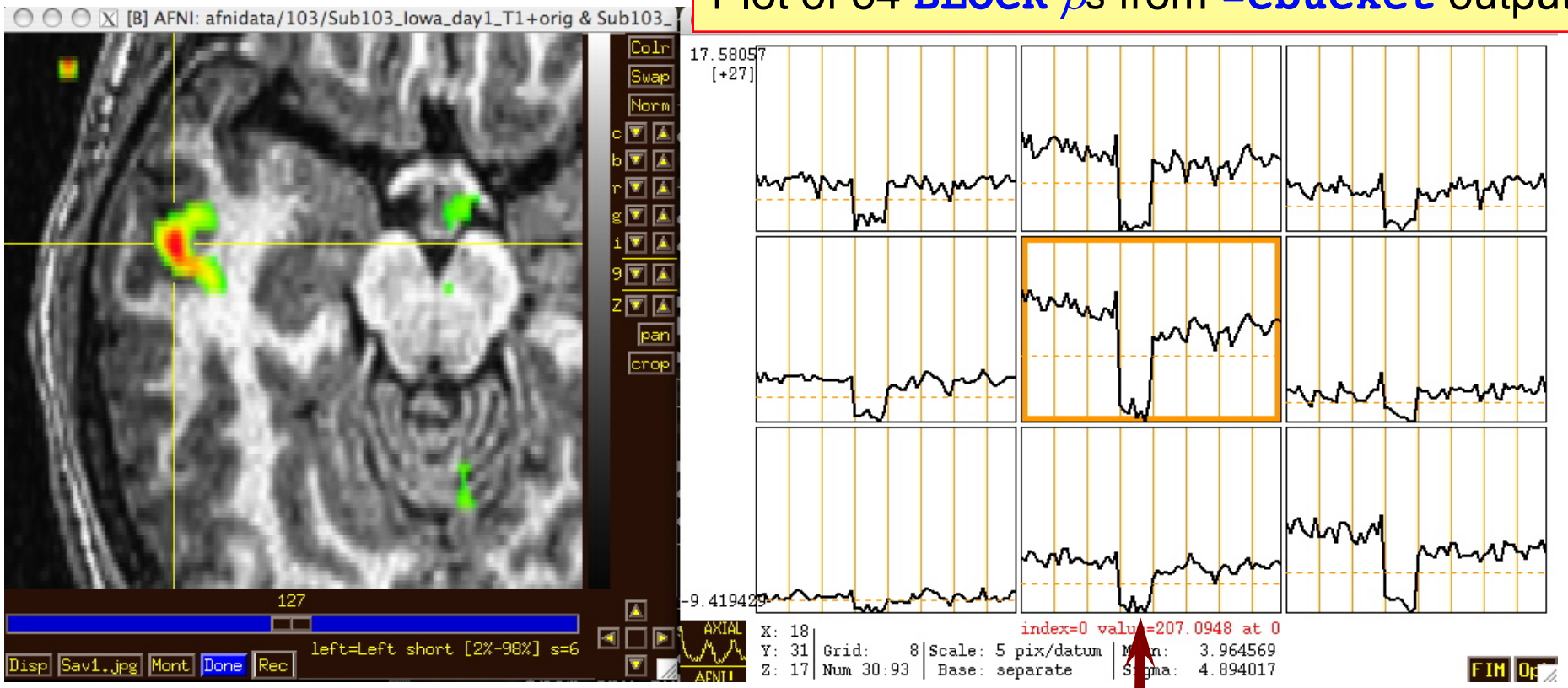
IM Regression - 1

- **IM** = **I**ndividual **M**odulation
  - Compute *separate* amplitude of response for each stimulus
    - Instead of computing average amplitude of responses to multiple stimuli in the same class
  - Response amplitudes (βs) for each individual block/event will be highly noisy
    - Can't use individual activation map for much
    - Must pool the computed βs in some further statistical analysis (*t*-test via `3dttest`? inter-voxel correlations in the βs? Correlate βs with something else?)
  - Usage: **`-stim_times_IM k tname model`**
    - Like **`-stim_times`**, but creates a separate regression matrix column for each time given

IM Regression - 2

- First application of IM was checking some data we received from another institution
- Experiment: 64 blocks of sensorimotor task (8 runs each with 8 blocks)

Plot of 64 **BLOCK** βs from **-cbucket** output



N.B.: sign reversal in run #4 = stimulus timing error!

AM Regression - 1

- **AM** = **A**mplitude **M**odulated (or Modulation)
  - Have some extra data measured about each response to a stimulus, and *maybe* the BOLD response amplitude is modulated by this
  - Reaction time; Galvanic skin response; Pain level perception; Emotional valence (happy or sad or angry face?)
- Want to see if some brain activations vary proportionally to this **ABI** (**A**uxiliary **B**ehaviorial **I**nformation)
- Discrete levels (2 or maybe 3) of ABI:
  - Separate the stimuli into sub-classes that are determined by the ABI ("on" and "off", maybe?)
  - Use a GLT to test if there is a difference between the FMRI responses in the sub-classes

```
3dDeconvolve ...                                                    \
 -stim_times 1 regressor_on.1D  'BLOCK(2,1)' -stim_label 1 'On'   \
 -stim_times 2 regressor_off.1D 'BLOCK(2,1)' -stim_label 2 'Off' \
 -gltsym 'SYM: +On | +Off' -glt_label 1 'On+Off'                   \
 -gltsym 'SYM: +On -Off'   -glt_label 2 'On-Off' ...
```

  - "`On+Off`" tests for any activation in *either* the "on" or "off" conditions
  - "`On-Off`" tests for differences in activation *between* "on" and "off" conditions
  - Can use `3dcalc` to threshold on ***both*** statistics at once to find a **conjunction**

AM Regression - 2

- Continuous (or several finely graded) ABI levels
  - Want to find active voxels whose activation level also depends on ABI
  - **3dDeconvolve** is a *linear* program, so must make the assumption that the change in FMRI signal as ABI changes is *linearly proportional* to the changes in the ABI values
- Need to make 2 separate regressors
  - One to find the mean FMRI response (the usual **-stim_times** analysis)
  - One to find the variations in the FMRI response as the ABI data varies
- The second regressor is $r_{\mathrm{AM2}}(t) = \sum_{k=1}^{K} h(t-\tau_k)\cdot(a_k - \bar{a})$
  - Where a_k =value of k^{th} ABI value, and a is the average ABI value
  - N.B.: If UNIX environment variable **AFNI_3Deconvolve_rawAM2** is set to **YES**, then mean of the a_k is not removed – for advanced users
- Response (β) for first regressor is standard activation map
- Statistics and β for second regressor make activation map of places whose BOLD response changes with changes in ABI
  - Using 2 regressors allows separation of voxels that are active but are *not* detectably modulated by the ABI from voxels that *are* ABI-sensitive

AM Regression - 3

- New feature of **3dDeconvolve**: **-stim_times_AM2**
- Use is very similar to standard **-stim_times**
  - **-stim_times_AM2 1 times_ABI.1D 'BLOCK(2,1)'**
  - The **times_ABI.1D** file has time entries that are "married" to ABI values:

```
10*5 23*4 27*2 39*5
17*2 32*5
*
16*2 24*3 37*5 41*4
```

  - Such files can be created from 2 standard ASCII .1D files using the new **1dMarry** program
    - The **-divorce** option can be used to split them up
- **3dDeconvolve** automatically creates the two regressors (unmodulated and amplitude modulated)
  - Use **-fout** option to get statistics for activation of pair of regressors (i.e., testing null hypothesis that *both* β weights are zero: that there is no ABI-independent *or* ABI-proportional signal change)
  - Use **-tout** option to test each β weight separately
  - Can **1dplot** $\mathbf{X}$ matrix columns to see each regressor

AM Regression - 4

- The **AM** feature is new-ish, and so needs more practical user experiences before it can be considered "standard practice"
  - In particular: don't know how much data or how many events are needed to get good ABI-dependent statistics
- If you want, **`-stim_times_AM1`** is also available
  - It only builds the regressor proportional to ABI data directly, with no mean removed:

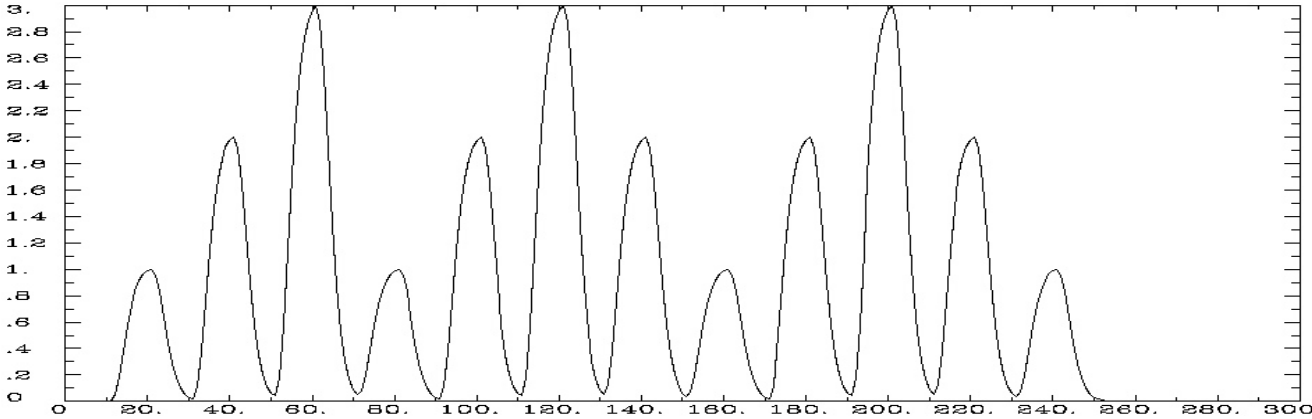
$$r_{\mathrm{AM1}}(t) = \sum_{k=1}^{K} h(t-\tau_k)\cdot a_k$$

  - Can't imagine what value this option has, but you never know … (if you can think of a good use, let me know) … We have one now [dmBLOCK]
- Future directions:
  - Allow more than one amplitude to be married to each stimulus time (insert obligatory polygamy/polyandry joke here) – this is done now
    - How many ABI types at once is too many? I don't know.
  - How to deal with unknown nonlinearities in the BOLD response to ABI values? I don't know. (Regress each event separately, then compute MI?)
  - Deconvolution with amplitude modulation? Requires more thought.

AM Regression - 5

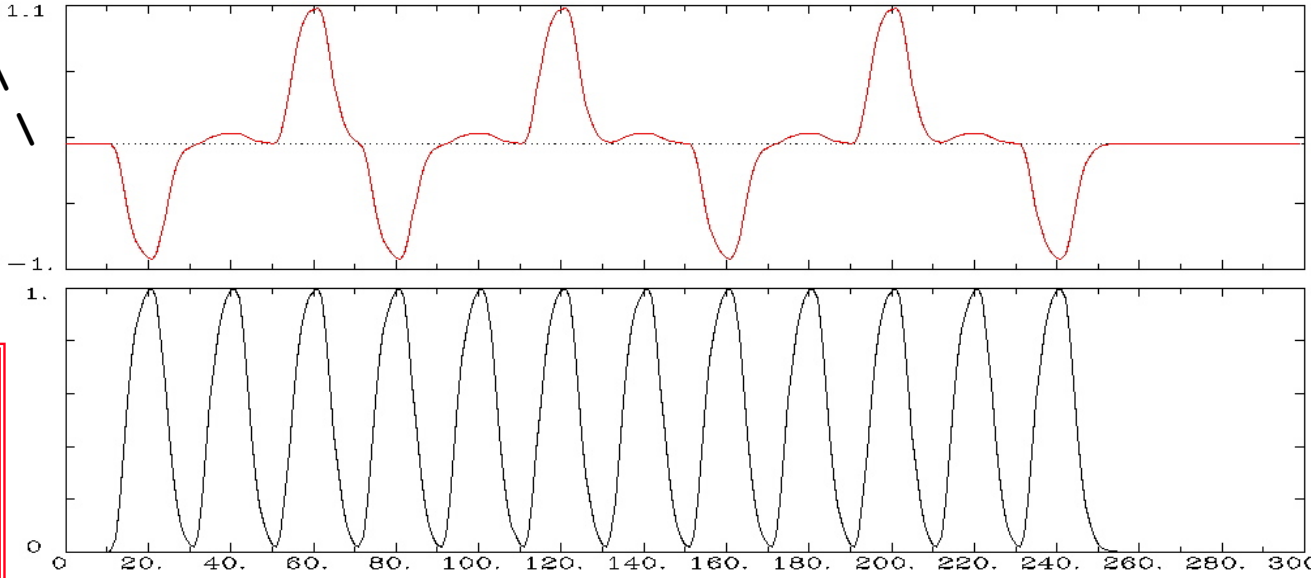
Timing: **AM.1D** = 10*1 30*2 50*3 70*1 90*2 110*3 130*2 150*1 170*2 190*3 210*2 230*1

- **3dDeconvolve -nodata 300 1.0 -num_stimts 1 **
  -stim_times_AM1 1 AM.1D 'BLOCK(10,1)' -x1D AM1.x1D
- **1dplot AM1.x1D'[2]'**



AM1 model of signal (modulation = ABI)

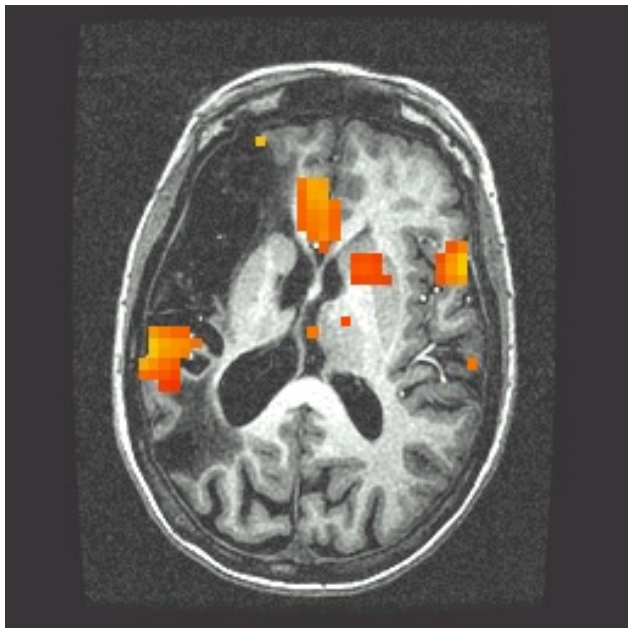
- **3dDeconvolve -nodata 300 1.0 **
  **-num_stimts 1 **
  **-stim_times_AM2 1 **
  **AM.1D 'BLOCK(10,1)' **
  -x1D AM2.x1D
- **1dplot -sepscl **
  AM2.x1D'[2,3]'

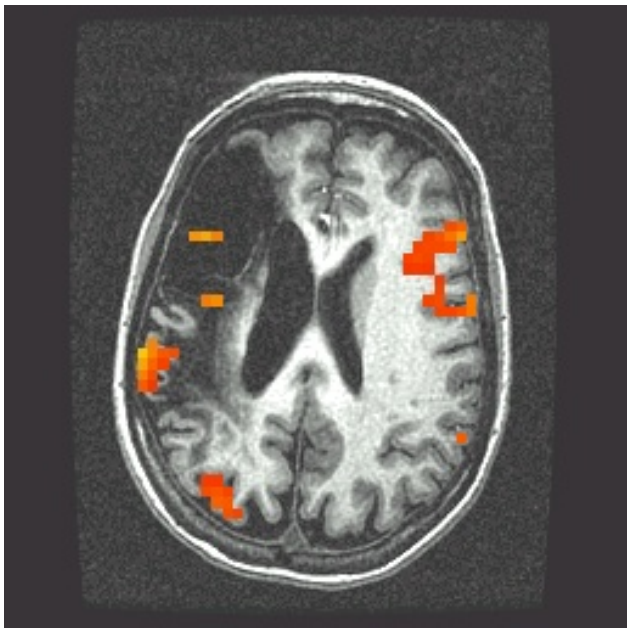


AM2 model of signal: is 2D sub-space spanned by these 2 time series

AM Regression - 6

- First actual user: Whitney Postman (formerly NIDCD; PI=Al Braun)
- Picture naming task in aphasic stroke patient
- ABI data = number of alternative names for each image (e.g., "balcony" & "porch" & "veranda", vs. "strawberry"), from 1 to 18
  - 8 imaging runs, 144 stimulus events
- 2 slices showing activation map for BOLD responses proportional to ABI (β_{AM2})
  - What does this mean? Don't ask me!



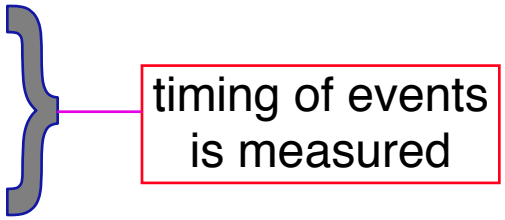


AM Regression - 7

- Alternative: use **IM** to get individual βs for each block/event and then do external regression statistics on those values
- Could do nonlinear fitting (to these βs) via **`3dNLfim`**, or inter-class contrasts via **`3dttest`**, **`3dLME`**, **`3dANOVA`**, or intra-class correlations via **`3dICC`**, etc.
- What is better: **AM** or **IM**+*something more* ?
  - We don't know – experience with these options is limited thus far – you can always try both!
  - If **AM** doesn't fit your models/ideas, then **IM**+ is clearly the way to go
  - Probably need to consult with AFNI group (SSCC) to get some hints/advice

More Complicated Experiment

- Solving a visually presented puzzle:
  a) subject sees puzzle
  b) subject cogitates a while
  c) subject responds with solution



- The problem is that we expect some voxels to be significant in phase (b) as well as phases (a) and/or (c)
- Variable length of phase (b) means that shape for its response varies between trials
  - Which is contrary to the whole idea of averaging trials together to get decent statistics (which is basically what linear regression for the β weights does, in an elaborate sort of way)
- Could assume response ***amplitude*** in phase (b) is constant across trials, and response ***duration*** varies directly with time between phases (a) and (c)
  - Need three HRFs
  - Can't generate (b) HRF in **`3dDeconvolve`**

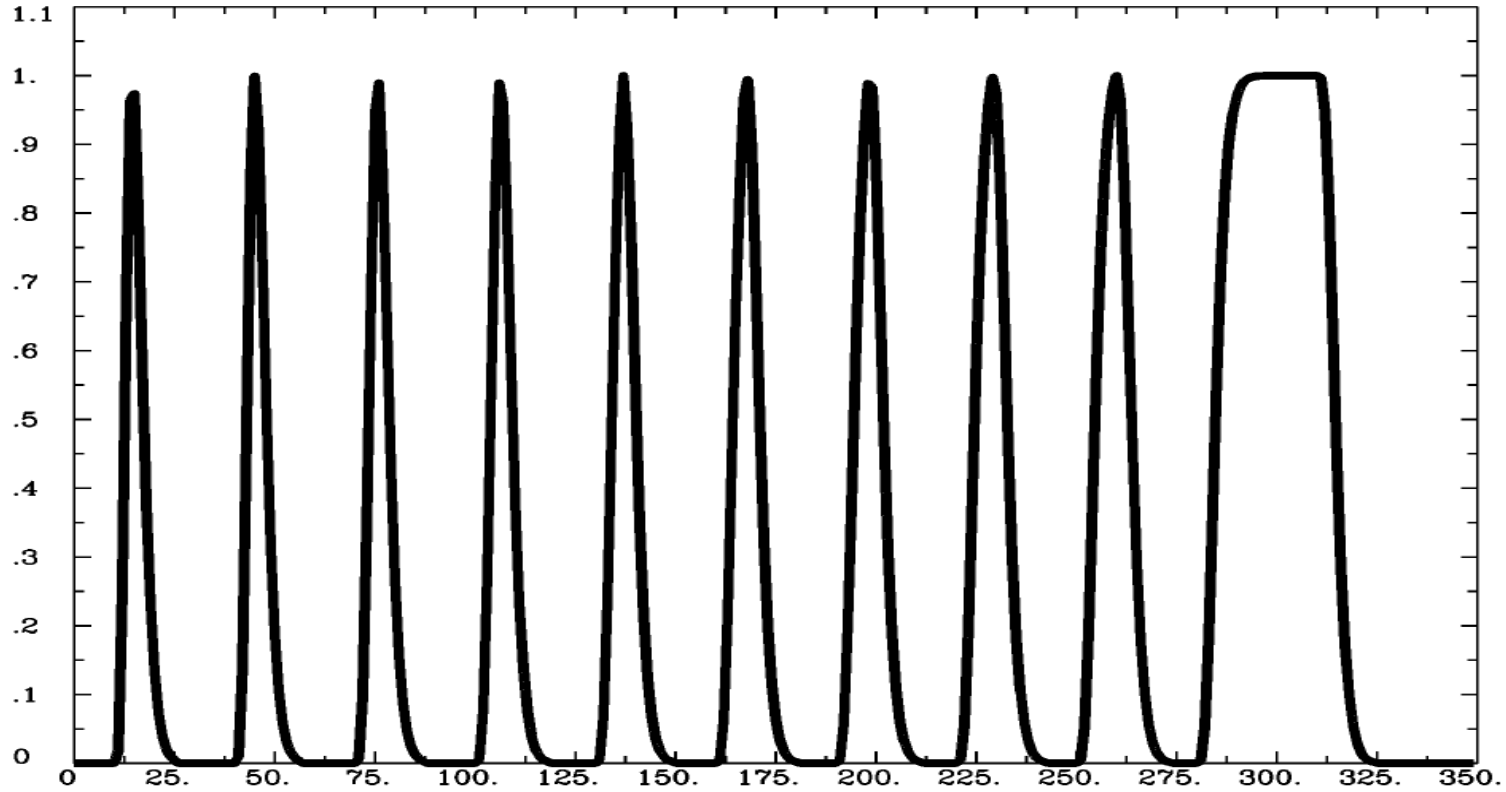
Yes we can!
`dmBLOCK` model

Duration Modulation (dm)

- When different stimuli in the same class have different (and known) durations
- Controlled by specifying the '**`dmBLOCK`**' response model
- Usually used with '**`-stim_times_AM1`**' to indicate that an extra parameter is *married* to each stimulus time
  - Here, parameter is the duration, not amplitude modulation
- You can also use '**`-stim_times_AM2`**' , by adding the extra amplitude modulation parameter(s)
  - The duration parameter for '**`dmBLOCK`**' is always the ***last*** parameter in a *marriage*
- For those unfortunates using data that is supplied with FSL-style 3-column stimulus files: "**`time duration amplitude`**"
  - You can use '**`-stim_times_FSL`**' to process these, without having to convert them to the AFNI format described herein
    - Which is like using '**`-stim_times_AM1`**'

- `3dDeconvolve -nodata 350 1 -polort -1 \`
  `-num_stimts 1 \`
  `-stim_times_AM1 1 q.1D 'dmBLOCK(1)' \`
  `-x1D stdout: | 1dplot -stdin -thick -thick`
- File `q.1D` contains 1 line:

10:1 40:2 70:3 100:4 130:5 160:6 190:7 220:8 250:9 280:30



Noise Issues

- "Noise" in FMRI is caused by several factors, not completely characterized
  - MR thermal noise (well understood, unremovable)
  - Cardiac and respiratory cycles (partly understood)
    - In principle, could measure these sources of noise separately and then try to regress them out
      - RETROICOR program
  - Scanner fluctuations (e.g., thermal drift of hardware, timing errors)
  - Small subject head movements (10-100 μm)
  - Very low frequency fluctuations (periods longer than 100 s)
- Data analysis should try to remove what can be removed and should allow for the statistical effects of what can't be removed
  - "Serial correlation" in the noise time series affects the *t*- and *F*-statistics calculated by `3dDeconvolve`
  - **Next slides**: AFNI program for dealing with this issue

Allowing for Serial Correlation

- *t*- and *F*-statistics denominators: estimates of noise variance
  - White noise estimate of variance:
    - *N* = number of time points
    - *m* = number of fit parameters
    - *N*–*m* = degrees of freedom = how many equal-variance independent random values are left after time series is fit with *m* regressors

$$\hat{\sigma}^2 = \frac{1}{N-m}\sum_{i=0}^{N-1}[\text{data}_i - \text{fit}_i]^2$$

- **Problem**: if noise values at successive time points are correlated, this estimate of variance is biased to be too small, since there aren't really *N*–*m* independent random values left
  - Denominator too small implies *t*- and *F*-statistics are too large!
  - And number of degrees of freedom is also too large.
  - So significance (*p*-value) of activations in individuals is overstated.
- **Solution #1**: estimate correlation structure of noise and then adjust statistics (downwards) appropriately
- **Solution #2**: estimate correlation structure of noise ***and*** also estimate ***β*** fit parameters using more efficient "generalized least squares", using this correlation, all at once (REML method)

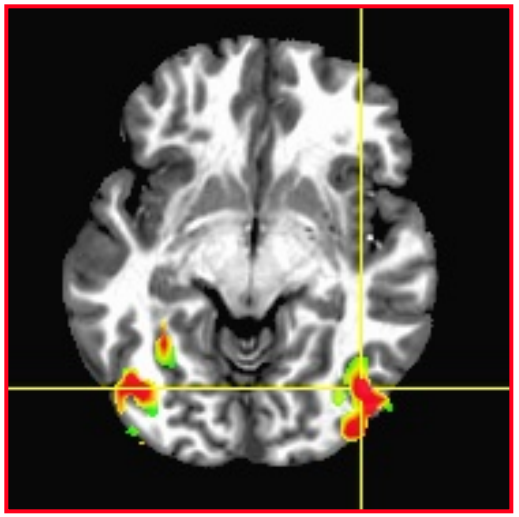
AFNI Program: `3dREMLfit`

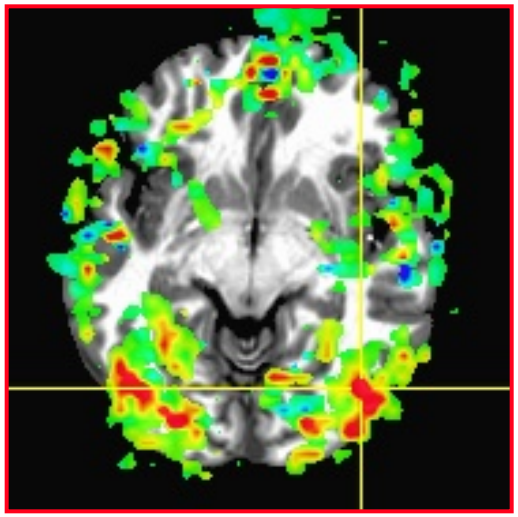
- Implements Solution #2
  - REML is a method for simultaneously estimating variance + correlation parameters ***and*** estimating regression fit parameters (***β***s)
  - Correlation structure of noise is ARMA(1,1)
    - 2 parameters ***a*** (AR) and ***b*** (MA) in each voxel
      - ***a*** describes how fast the noise de-correlates over time
      - ***b*** describes the short-range correlation in time (1 lag)
    - Unlike SPM and FSL, *each voxel* gets a separate estimate of its own correlation parameters
- Inputs to `3dREMLfit`
  - run `3dDeconvolve` first to setup `.xmat.1D` matrix file and GLTs (don't have to let `3dDeconvolve` finish analysis: `-x1D_stop`)
    - `3dDeconvolve` also outputs a command line to run `3dREMLfit`
  - then, input matrix file and 3D+time dataset to `3dREMLfit`
- Output datasets are similar to those in `3dDeconvolve`

Sample Outputs

- Compare with **AFNI_data3/afni/rall_regress results**
- **3dREMLfit -matrix rall_xmat.x1D -input rall_vr+orig -fout -tout **
  **-Rvar rall_varR -Rbuck rall_funcR -Rfitts rall_fittsR **
  -Obuck rall_funcO -Ofitts rall_fittsO

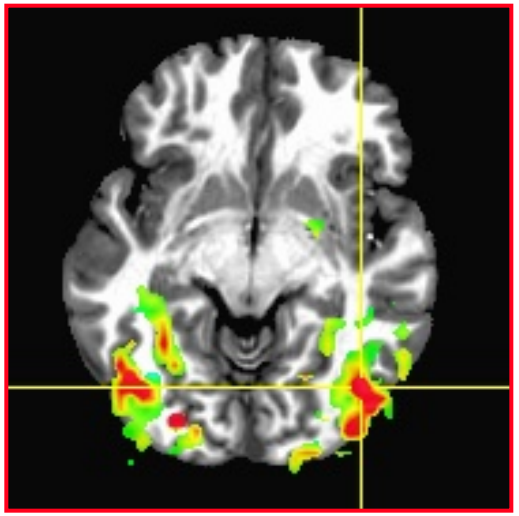
REML
F=3.15
p=0.001

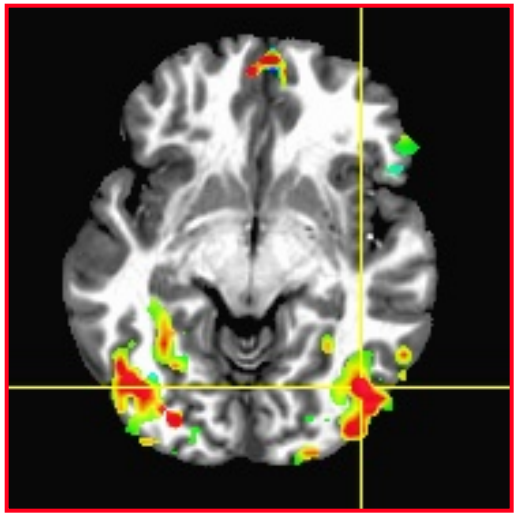




OLSQ
F=3.15
p=0.001

REML
F=1.825
p=0.061
- *F* = No activity outside brain!





OLSQ
F=5.358
p=5e-7
- *F* = No activity outside brain!

Oh My GOD *!?!*

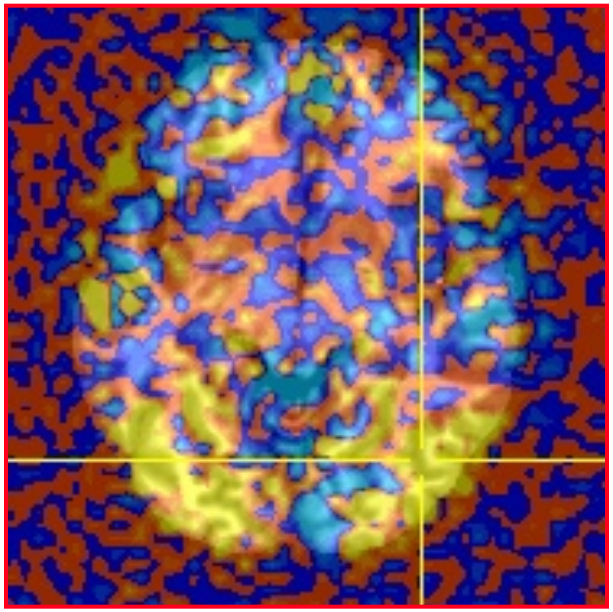
It's Not So Bad: β !

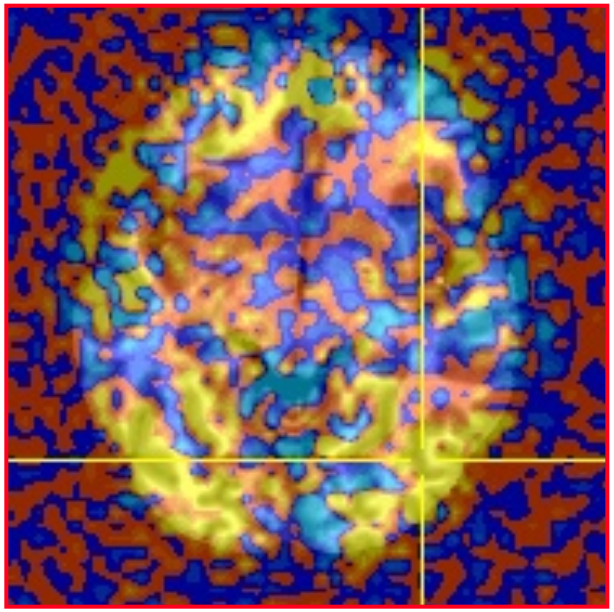
- For individual activation maps, `3dREMLfit`-ized *t*- and *F*-statistics are significantly different, and more accurate
- But … There are at present very few applications for such individual FMRI activation maps
  - pre-surgical planning; some longitudinal study?
- For standard group analysis, inputs are only β fit parameters
  - Which don't change so much between REML and OLSQ

Color Overlay = β weight from analysis on previous slide, no threshold

REML

CPU 500 s





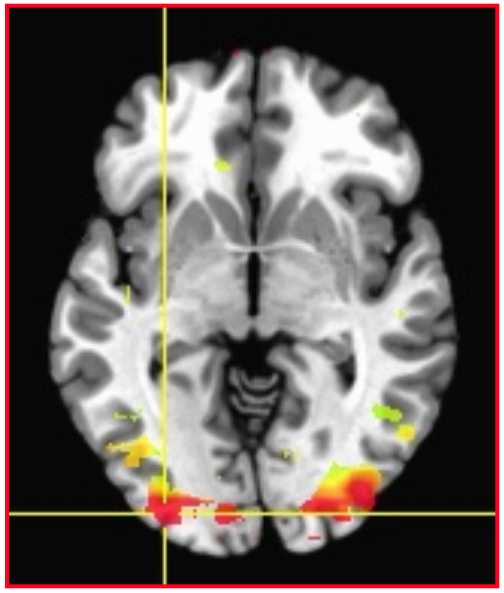
OLSQ

CPU 156 s

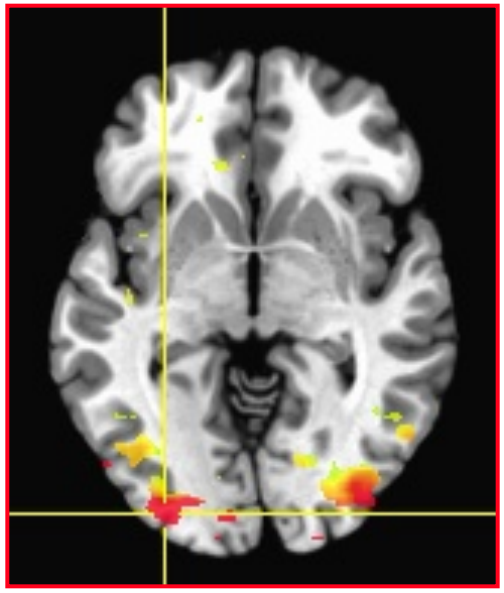
It's Not So Bad At All: Group Analysis!

- Group analysis activation maps (`3dANOVA3`) from 16 subjects

REML



OLSQ



***F*-test for Affect condition**

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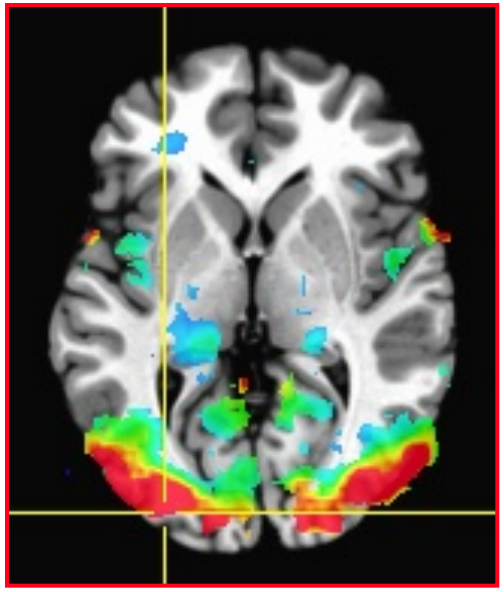

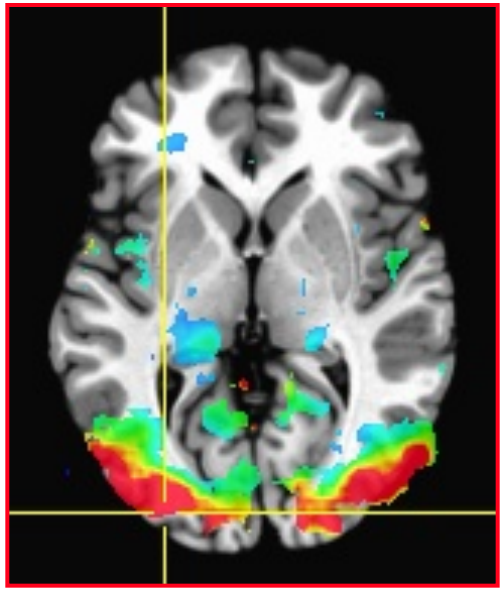

***F*-test for Category condition**

***F*-test for Category condition**

Nonlinear Regression

- Linear models aren't the only possibility
  - e.g., could try to fit HRF of the form $h(t) = a \cdot t^b \cdot e^{-t/c}$
  - Unknowns b and c appear nonlinearly in this formula
- Program **`3dNLfim`** can do nonlinear regression (including nonlinear deconvolution)
  - User must provide a C function that computes the model time series, given a set of parameters (e.g., a, b, c)
    - We could help you develop this C model function
    - Several sample model functions in the AFNI source code distribution
  - Program then drives this C function repeatedly, searching for the set of parameters that best fit each voxel
  - Has been used to fit pharmacological wash-in/wash-out models (difference of two exponentials) to FMRI data acquired during pharmacological challenges
    - e.g., injection of nicotine, cocaine, ethanol, etc.
    - these are difficult experiments to do ***and*** to analyze

Spatial Models of Activation

- Smooth data in space before analysis

- Average data across anatomically-selected regions of interest ROI (before or after analysis)
  - Labor intensive (*i.e.*, hire more students)
  - *Or* could use ROIs from atlases, *or* from FreeSurfer per-subject parcellation

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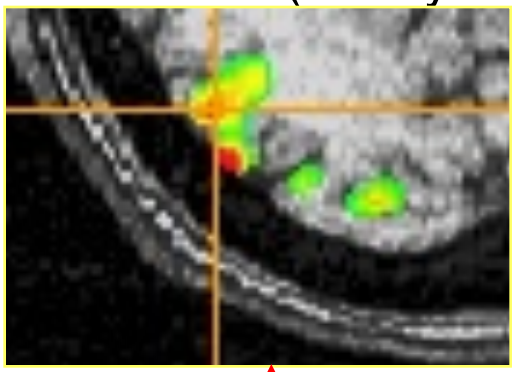
- Reject isolated small clusters of above-threshold voxels after analysis

Spatial Smoothing of Data

- Reduces number of comparisons
- Reduces noise (by averaging)
- Reduces spatial resolution
  - Blur it enough: Can make FMRI results look like low resolution (1990s) PET data
- Smart smoothing: average ***only*** over nearby brain or gray matter voxels
  - Uses resolution of FMRI cleverly
    - **`3dBlurToFWHM`** and **`3dBlurInMask`**
  - *Or*, average over selected ROIs
  - *Or*, cortical surface based smoothing
- Estimate smoothness with **`3dFWHMx`**

3dBlurToFWHM & 3dBlurInMask

- Program to smooth FMRI time series datasets to a specified smoothness (as estimated by FWHM of noise spatial correlation function)
  - Don't just add smoothness (à la **3dmerge**) but control it (locally and globally)
  - Goal: use datasets from diverse scanners



- Why blur FMRI time series?
  - Averaging neighbors will reduce noise
  - Activations are (usually) blob-ish (several voxels across)
  - Diminishes the multiple comparisons problem
- **3dBlurToFWHM** and **3dBlurInMask** blur only inside a mask region
  - To avoid mixing air (noise-only) and brain voxels
  - Partial Differential Equation (PDE) based blurring method
    - 2D (intra-slice) or 3D blurring

Multi-Voxel Statistics

Spatial Clustering
&
False Discovery Rate:

"Correcting" the Significance

Basic Problem

- Usually have 50-200K FMRI voxels in the brain
- Have to make at least one decision about each one:
  - Is it "active"?
    - That is, does its time series match the temporal pattern of activity we expect?
  - Is it differentially active?
    - That is, is the BOLD signal change in task #1 different from task #2?
- Statistical analysis is designed to control the error rate of these decisions
  - Making ***lots*** of decisions: hard to get perfection in statistical testing

- **Family-Wise Error (FWE)**
  - Multiple testing problem: voxel-wise statistical analysis
    - With N voxels, what is the chance to make a false positive error (Type I) in one or more voxels?

      Family-Wise Error: $\alpha_{FW} = 1-(1-p)^N \rightarrow 1$ as N increases
    - For Np small (compared to 1), $\alpha_{FW} \approx Np$
    - $N \approx 50{,}000+$ voxels in the brain
    - To keep probability of even one false positive $\alpha_{FW} < 0.05$ (the "corrected" p-value), need to have $p < 0.05/5\times10^4 = 10^{-6}$
    - This constraint on the per-voxel ("uncorrected") p-value is so stringent that we would end up rejecting a lot of true positives (Type II errors) also, just to control the overall Type I error rate
- Multiple testing problem in FMRI
  - 3 occurrences of multiple tests: Individual, Group, and Conjunction
  - Group analysis is the most severe situation (have the least data, considered as number of independent samples = subjects)

- **Two Approaches to the "Curse of Multiple Comparisons"**
  - Control FWE to keep expected total number of false positives below 1
    - Overall significance: α_{FW} = Prob(≥ one false positive voxel in the whole brain)
    - **Bonferroni correction**: $\alpha_{FW} = 1-(1-p)^N \approx Np$, if $p << N^{-1}$
      - Use $p = \alpha/N$ as individual voxel significance level to achieve $\alpha_{FW} = \alpha$
      - Too stringent and overly conservative: $p = 10^{-8} \ldots 10^{-6}$
    - What can rescue us from this hell of statistical super-conservatism?
      - Correlation: Voxels in the brain are not independent
        - Especially after we smooth them together!
        - Means that Bonferroni correction is *way* ***way*** too stringent
      - Contiguity: Structures in the brain activation map
        - We are looking for activated "blobs": the chance that pure noise (H_0) will give a set of seemingly-activated voxels next to each other is lower than getting false positives that are scattered around far apart
      - Control FWE based on spatial correlation (smoothness of image noise) **and** minimum cluster size we are willing to accept

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  - Control false discovery rate (FDR) — Much more on this a little later!
    - FDR = expected proportion of false positive voxels among all detected voxels
      - Give up on the idea of having (almost) no false positives at all

False Discovery Rate in AFNI

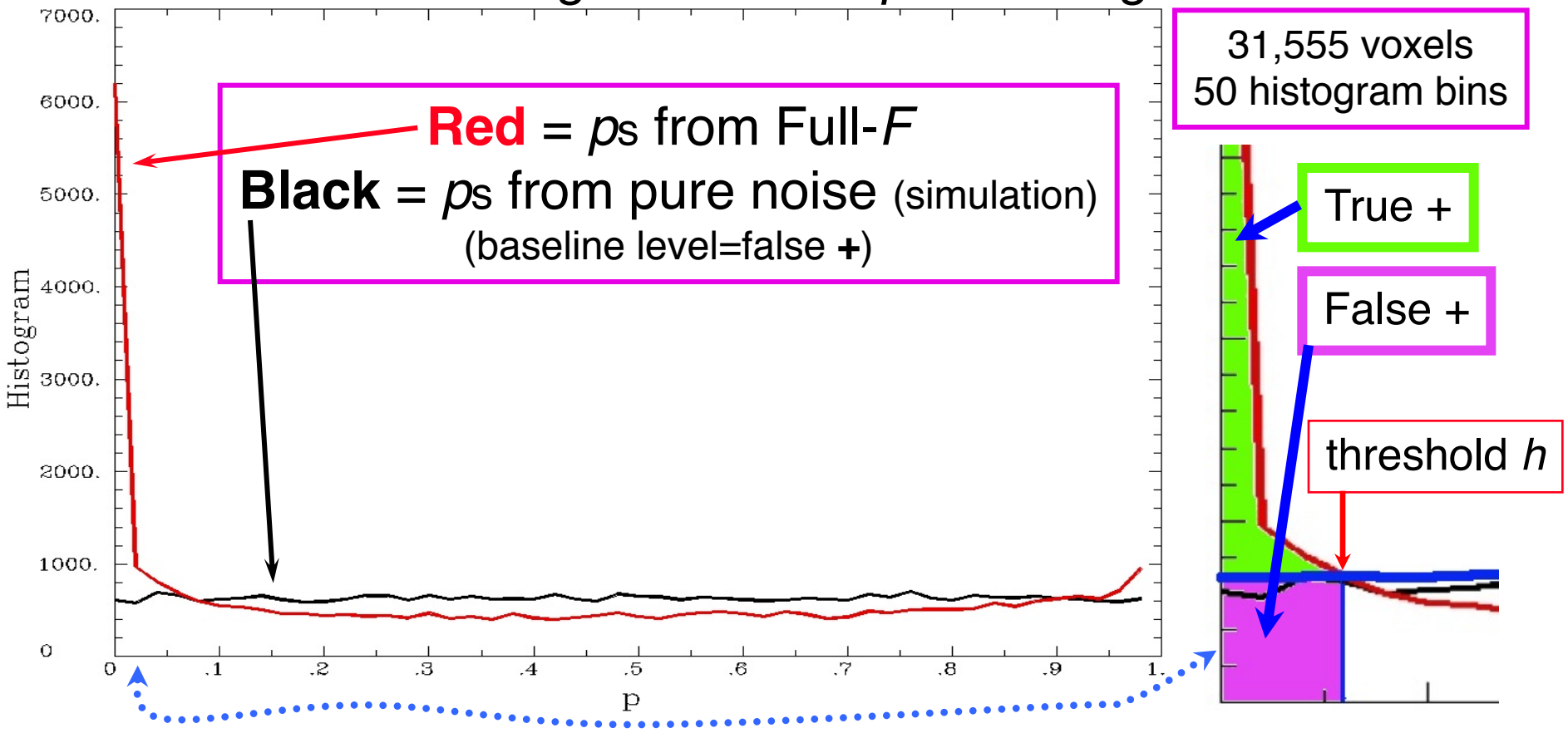
- Situation: making *many* statistical tests at once
  - e.g, Image voxels in FMRI; associating genes with disease
- Want to set threshold on statistic (e.g., *F*- or *t*-value) to control ***false positive*** error rate
- Traditionally: set threshold to control probability of making a ***single*** false positive detection
  - But if we are doing 1000s (or more) of tests at once, we have to be very stringent to keep this probability low
- **FDR**: accept the fact that there will be multiple erroneous detections when making lots of decisions
  - Control the ***fraction*** of positive detections that are wrong
    - Of course, no way to tell which individual detections are right!
  - Or at least: control the *expected value* of this fraction

FDR: q [and $z(q)$]

- Given some collection of statistics (say, *F*-values from **`3dDeconvolve`**), set a threshold *h*
- The **uncorrected *p*-value** of *h* is the probability that $F > h$ when the null hypothesis is true (no activation)
  - "Uncorrected" means "per-voxel"
  - The "corrected" *p*-value is the probability that *any* voxel is above threshold in the case that they are all *un*activated
  - If have *N* voxels to test, $p_{\text{corrected}} = 1-(1-p)^N \approx Np$ (for small *p*)
    - Bonferroni: to keep $p_{\text{corrected}} < 0.05$, need $p < 0.05 / N$, which is very tiny
- The FDR ***q*-value** of *h* is the fraction of false positives expected when we set the threshold to *h*
  - Smaller *q* is "better" (more stringent = fewer false detections)
  - $z(q)$ = conversion of *q* to Gaussian *z*: e.g, $z(0.05) \approx 1.95996$
    - So that larger is "better" (in the same sense) e.g, $z(0.01) \approx 2.57583$

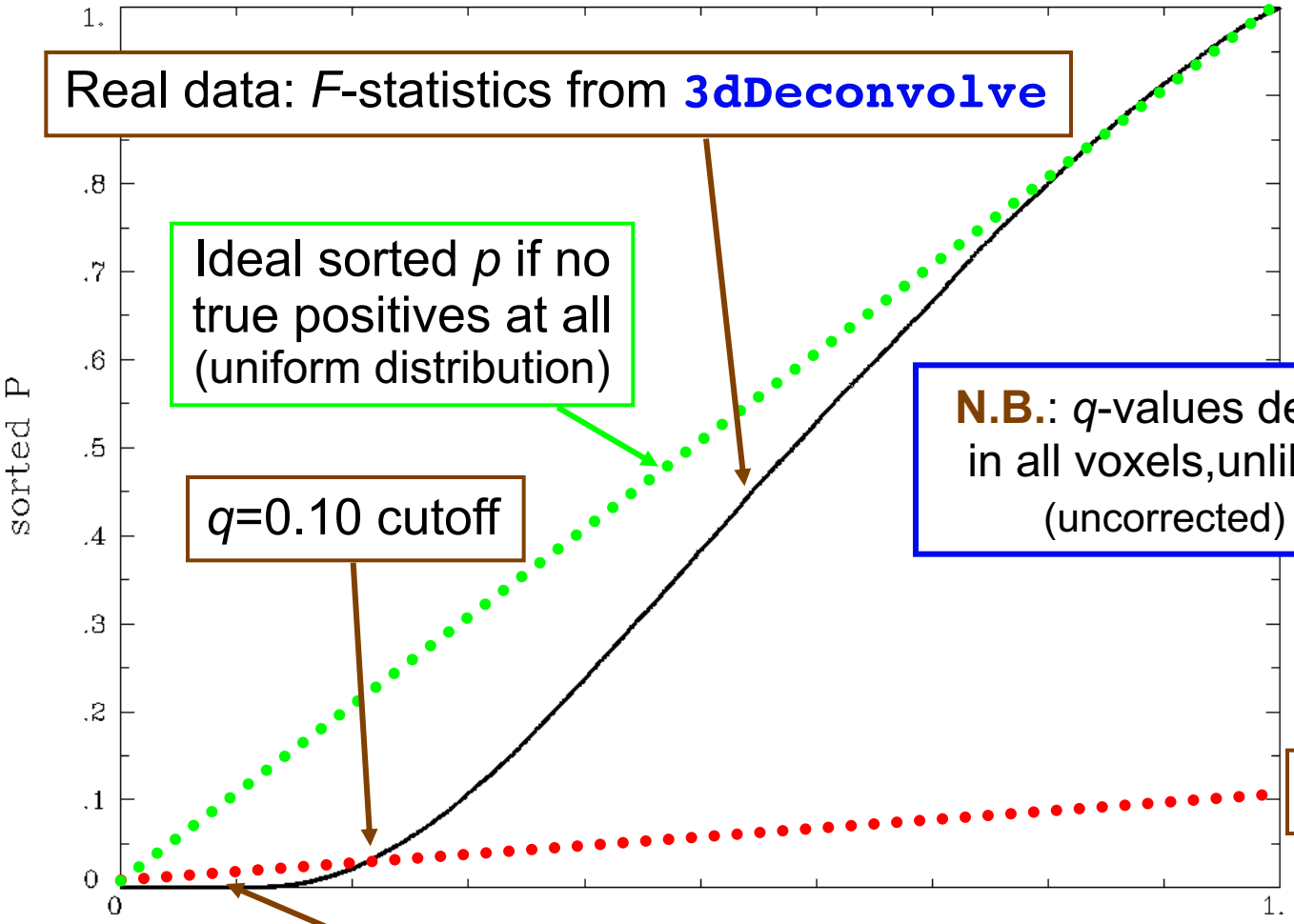
Basic Ideas Behind FDR *q*

- ***If*** all the null hypotheses are true, ***then*** the statistical distribution of the *p*-values will be uniform
  - Deviations from uniformity at low *p*-values ➔ true positives
  - Baseline of uniformity indicates how many true negatives are hidden amongst in the low *p*-value region



Graphical Calculation of *q*

- Graph sorted *p*-values of voxel #*k* vs. $\zeta = k/N$ (the cumulative histogram of *p*, flipped sideways) and draw some lines from origin



Real data: *F*-statistics from **3dDeconvolve**

Ideal sorted *p* if no true positives at all (uniform distribution)

q=0.10 cutoff

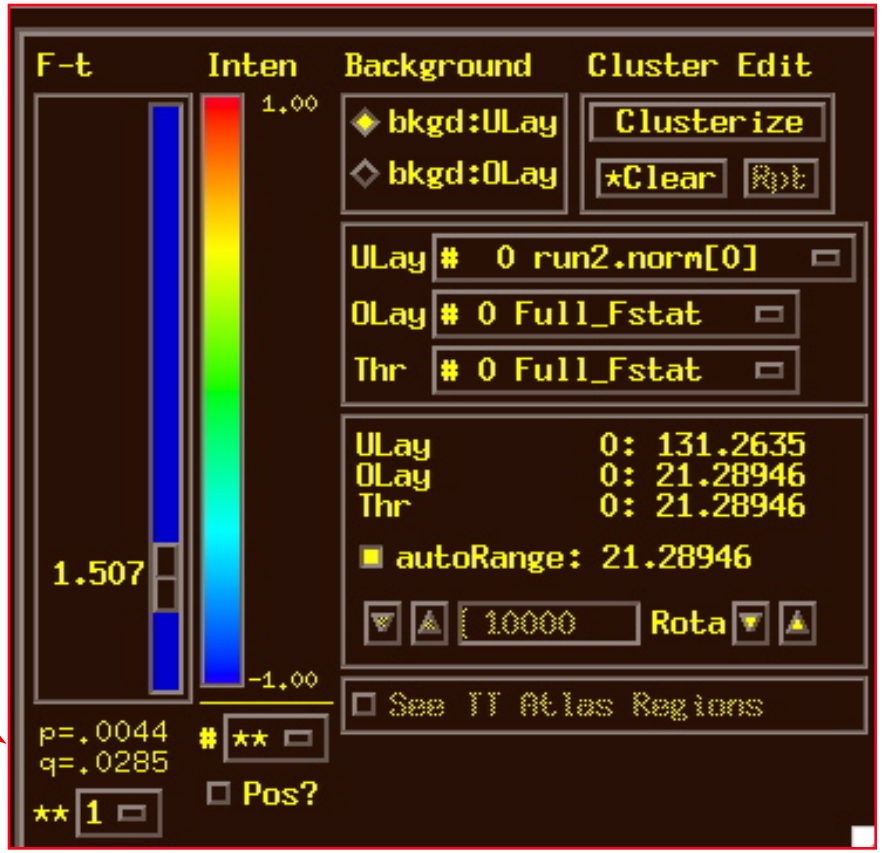
N.B.: *q*-values depend on data in all voxels,unlike voxel-wise (uncorrected) *p*-values*!*

Slope=0.10

Very small *p* = very significant

FDR curves: *h* vs. *z*(*q*)

- **3dDeconvolve**, **3dANOVAx**, **3dttest**, and **3dNLfim** now compute FDR curves for all statistical sub-bricks and store them in output header
- **3drefit -addFDR** does same for other datasets
  - **3drefit -unFDR** can be used to delete such info
- **AFNI** now shows *p*- **and** *q*-values below the threshold slider bar
  - Interpolates FDR curve from header (threshold➔*z*➔*q*)
    - Can be used to adjust threshold by "eyeball"



q = N/A means it's not available

MDF hint = "missed detection fraction"

FDR Statistical Issues

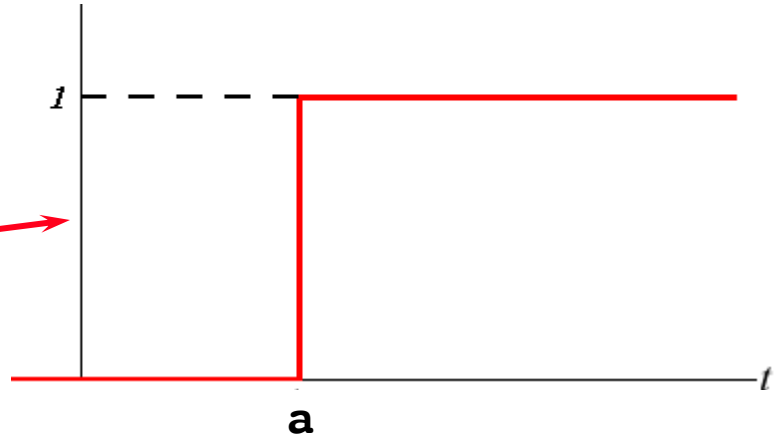
- FDR is conservative (*q*-values are too large) when voxels are positively correlated (e.g., from spatially smoothing)
  - Correcting for this is not so easy, since *q* depends on data (including true positives), so a simulation like **`3dClustSim`** is hard to conceptualize
  - At present, FDR in AFNI is an alternative way of controlling false positives, vs. **`3dClustSim`** (clustering)
- Accuracy of FDR calculation depends on *p*-values being uniformly distributed under the null hypothesis
  - Statistic-to-*p* conversion should be accurate, which means that null *F*-distribution (say) should be correctly estimated
  - Serial correlation in FMRI time series means that **`3dDeconvolve`** denominator DOF is too large
  - ➔ *p*-values will be too small, so *q*-values will be too small
    - **`3dREMLfit`** rides to the rescue*!*

FWE or FDR?

- These 2 methods control Type I error in different senses
  - FWE: α_{FW} = Prob (≥ one false positive voxel/cluster in the whole brain)
    - Frequentist's perspective: Probability among **many** hypothetical activation maps gathered under identical conditions
    - Advantage: can directly incorporate smoothness into estimate of α_{FW}
  - FDR = expected fraction of false positive voxels among all detected voxels
    - Focus: controlling false positives among detected voxels in **one** activation map, as given by the experiment at hand
    - Advantage: not afraid of making a few Type I errors in a large field of true positives
  - Concrete example
    - Individual voxel $p = 0.001$ for a brain of 50,000 EPI voxels
    - Uncorrected → ≈50 false positive voxels in the brain
    - FWE: corrected $p = 0.05$ → ≈5% of the time would expect one or more purely false positive clusters in the entire volume of interest
    - FDR: $q = 0.05$ → ≈5% of voxels among those positively labeled ones are false positive
- What if your favorite blob (activation area) fails to survive correction?
  - Tricks (don't tell anyone we told you about these)
    - One-sided *t*-test? NN=3 clustering?
    - ROI-based statistics – e.g., grey matter mask, or whatever regions you focus on
  - Analysis on surface; *or*, Use better group analysis tool (**`3dLME`**, **`3dMEMA`**, etc.)

Conjunction Analysis

- **Conjunction**
  - Dictionary: "a compound proposition that is true if and only if all of its component propositions are true"
  - FMRI: areas that are active under 2 or more conditions (**`AND`** logic)
    - e.g, in a visual language task and in an auditory language task
  - In FMRI papers: Is also be used to mean analysis to find areas that are exclusively activated in one task but not another (**`XOR`** logic) or areas that are active in either task (non-exclusive **`OR`** logic) – technically *disjunctions*
  - If have *n* different tasks, have 2^n possible combinations of activation overlaps in each voxel (ranging from nothing there to complete overlap)
  - Tool: **`3dcalc`** applied to statistical maps
    - Heaviside step function defines a *On/Off* logic
    - **`step(t-a)`** = 0 if **`t`** < **`a`**
= 1 if **`t`** > **`a`**
    - Can be used to apply more than one threshold at a time

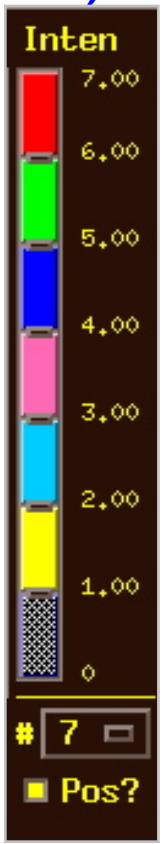


- Example of forming all possible "conjunctions"
  - 3 contrasts/tasks A, B, and C, each with a *t*-stat from **`3dDeconvolve`**
  - Assign each a number, based on binary positional notation:
    - A: $001_2 = 2^0 = \mathbf{1}$; B: $010_2 = 2^1 = \mathbf{2}$; C: $100_2 = 2^2 = \mathbf{4}$
  - Create a mask using 3 sub-bricks of *t* (*e.g.*, threshold = 4.2)

```
3dcalc -a ContrA+tlrc -b ContrB+tlrc -c ContrC+tlrc \
-expr '1*step(a-4.2)+2*step(b-4.2)+4*step(c-4.2)'   \
-prefix ConjAna
```

  - Interpret output, which has 8 possible (=2^3) scenarios:

$000_2 = \mathbf{0}$: none are active at this voxel
$001_2 = \mathbf{1}$: A is active, but no others
$010_2 = \mathbf{2}$: B, but no others
$011_2 = \mathbf{3}$: A and B, but not C
$100_2 = \mathbf{4}$: C but no others
$101_2 = \mathbf{5}$: A and C, but not B
$110_2 = \mathbf{6}$: B and C, but not A
$111_2 = \mathbf{7}$: A, B, and C are all active at this voxel



Can display each combination with a different color and so make pretty pictures that *might* even mean something**!**

- **Multiple testing correction issue**
  - How to calculate the *p*-value for the conjunction map?
  - No problem, ***if*** each entity was corrected (e.g., cluster-size thresholded at *t*=4.2) before conjunction analysis, via **`3dClustSim`**
  - But that may be too stringent (conservative) and over-corrected
  - With 2 or 3 entities, analytical calculation of conjunction p_{conj} is possible
    - Each individual test can have different uncorrected (per-voxel) *p*
    - Double or triple integral of tails of non-spherical (correlated) Gaussian distributions — not available in simple analytical formulae
  - With more than 3 entities, may have to resort to simulations
    - Monte Carlo simulations? (AKA: Buy a fast computer)
    - Will Gang Chen write such a program? Only time will tell!