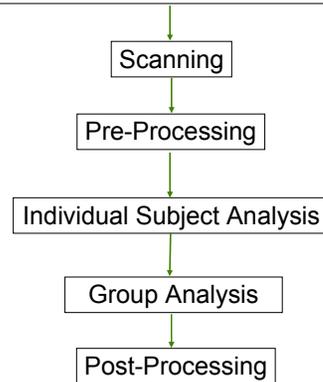


## FMRI Analysis

### Experiment Design



### Scheme of the Talk

- Design Types
  - Block
  - Event-related
  - Mixed
- Players in Experiment Design
  - BOLD signal: not direct measure of neuronal activities
  - Contrasts
- Intuitive Thinking
  - Usable bandwidth for FMRI data
- Statistical Theory
  - Efficiency
- Experiment Design in AFNI
  - AlphaSim and 3dDeconvolve
- Miscellaneous

### Design Types

- Event-related design
  - Instant stimulus
  - Modeling options
    - Prefixed shape
    - Whatever fits: deconvolution
    - Basis functions
- Block design
  - Conditions with significant durations
  - Other terminologies: Epoch, box-car
  - Usually model with prefixed-shape HRF, but may also model with
    - deconvolution approach for flexible shapes
    - multiple events for each block: allow amplitude attenuation
- Mixed design
- ISI, SOA, etc.

### Players in Experiment Design

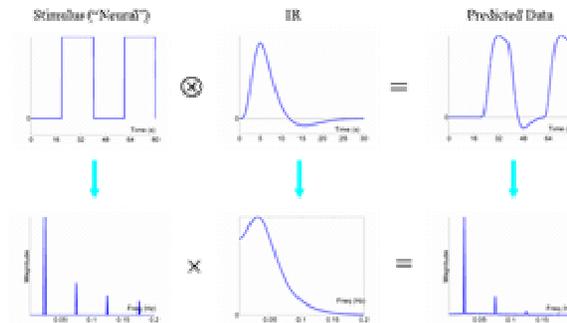
- Number of subjects ( $n$ )
  - Important for group analysis: inter-subject vs. intra-subject variation
  - Power roughly proportional to  $\sqrt{n}$
  - Recommended: 20+; Current practice: 12 – 20
- Number of time points
  - Important for individual subject analysis
  - Power proportional to  $\sqrt{DF}$
  - Limited by subject's tolerance in scanner: 30-90 min per session
- TR length
  - Shorter TR yields more time points (and potentially more power)
  - Power improvement limited by stronger temporal correlation and weaker MR signal
  - Usually limited by hardware considerations

## Players in Experiment Design

- **Design of the study**
  - Complexity: factors, levels, covariate, contrasts of interest, balance of events/levels/subjects...
  - Design choices may limit statistical analysis options
- **Number of events per class**
  - The more the better (20+), but no magic number
- **HRF modeling**
  - Conservative, liberal, or middle
- **Event arrangement**
  - How to design? How to define 'best' design?
  - Efficiency: achieve highest power within fixed scanning time

## Intuitive Thinking

- **Classical HRF**
  - Convolution in time = multiplication in frequency



## Intuitive Thinking

- **Event frequency**
  - Optimal frequency: 0.03 Hz (period 30 s)
    - Implication for block designs: optimal duration – about 15s
  - Upper bound: 0.15 Hz (6.7 s)
    - Submerged in the sea of white noise
    - Implication for event-related designs: average ISI > 6s
  - Lower bound: 0.01 Hz (100 s)
    - Confounded with trend or removed by high-pass filtering
    - Implication for block designs: maximum duration about 50s\*
      - \*Longer blocks could still be analyzed (see last slide)
  - Bandwidth: 0.01 – 0.15 Hz
    - Spread events within the frequency window (next topic)

## Statistical Theory

- **Regression Model (GLS)**
  - $Y = X\beta + \varepsilon$ ,  $X$ : design matrix with columns of regressors
- **General Linear testing**
  - One test  $H_0: c'\beta = 0$  with  $c = (c_0, c_1, \dots, c_p)$ 
    - $t = c'\beta / \sqrt{[c'(X'X)^{-1}c] \text{MSE}}$  (MSE: unknown but same across tests)
      - Signal-to-noise ratio
      - Effect vs. uncertainty
    - $\sqrt{c'(X'X)^{-1}c}$ : normalized standard deviation of contrast  $c'\beta$ 
      - Efficiency =  $1/\sqrt{c'(X'X)^{-1}c}$ : Smaller  $\rightarrow$  more powerful (and more efficient)
      - $X'X$  measures the co-variation among the regressors: Less correlated regressors are more efficient and easier to tease regressors apart
      - $X'X$  magnifies the uncertainty due to noise
    - Goal: find a design ( $X$ ) that renders low norm. std. dev.

## Statistical Theory

- General Linear testing
  - Multiple tests:
    - $H_{01}: c_1'\beta = 0$  with  $c = (c_{10}, c_{11}, \dots, c_{1p}), \dots$
    - $H_{0k}: c_k'\beta = 0$  with  $c = (c_{k0}, c_{k1}, \dots, c_{kp})$
  - Efficiency (sensitivity): a relative value; dimensionless
    - > in AFNI:  $1/\sum$  individual norm. std dev.'s
    - >  $\sum$  individual efficiencies
  - Find efficient design
    - > Minimizing  $\sum$  individual norm. std dev.'s
    - > Minimizing the maximum of individual norm. std dev.'s

## Experiment Design in AFNI

- AFNI programs for designing event-related experiments
  - **RSFgen**: Design  $X$  by generating randomized events
  - `make_stim_times.py`: convert stimulus coding to timing
  - **3dDeconvolve -nodata**: calculate efficiency
- Toy example: experiment parameters
  - TR = 2s, 300 TR's, 3 stimulus types, 50 repetitions for each type
  - On average
    - One event of a type every 6 TR's
    - ISI = 12 TR's
    - frequency = 0.083 Hz

## Experiment Design in AFNI

- Toy example: Design an experiment and check its efficiency
  - TR = 2s, 300 TR's, 3 event types (A, B, and C), 50 repetitions each
  - 3 tests of interest: A-B, A-C, and B-C
  - Modeling approach: prefixed or whatever fits?
  - Go to directory `AFNI_data1/ht03`
  - **1st step**: generate randomized events – script `s1.RSFgen` – by shuffling 50 1's, 50 2's, 50 3's, and 150 0's:

```
RSFgen -nt 300 -num_stimts 3 \
      -nreps 1 50 -nreps 2 50 -nreps 3 50 \
      -seed 2483907 -prefix RSFstim.
```

- Output: `RSFstim.1.1D RSFstim.2.1D RSFstim.3.1D`
- Check the design by plotting the events
  - `ldplot `ls RSFstim.*.1D` &`

## Experiment Design in AFNI

- Toy example: Design an experiment and check its efficiency
  - TR = 2s, 300 TR's, 3 stimulus types, 50 repetitions for each type
  - **2nd step**: Convert stimulus coding into timing (`s2.StimTimes`)

```
make_stim_times.py -prefix stim -nt 300 -tr 2 -nruns 1 \
  -files RSFstim.1.1D RSFstim.2.1D RSFstim.3.1D
```

- Output: `stim.01.1D stim.02.1D stim.03.1D`
- Check the timing files, e.g.
  - `more stim.01.1D`

## Experiment Design in AFNI

- Toy example: Design an experiment and check its efficiency
  - 3rd step: Calculate efficiency for each contrast (`s3.Efficiency`)

```
set model = GAM # toggle btw GAM and 'TENT(0,12,7)'
3dDeconvolve -nodata 300 2 -nfirst 4 -nlast 299 \
  -polort 2 -num_stims 3 \
  -stim_times 1 "stim.01.1D" "$model" \
  -stim_label 1 "stimA" \
  -stim_times 2 "stim.02.1D" "$model" \
  -stim_label 2 "stimB" \
  -stim_times 3 "stim.03.1D" "$model" \
  -stim_label 3 "stimC" \
  -gltsym "SYM: stimA -stimB" \
  -gltsym "SYM: stimA -stimC" \
  -gltsym "SYM: stimB -stimC"
```

3 regressors

3 contrasts

## Experiment Design in AFNI

- Toy example: Design an experiment and check its efficiency
  - Third step: Calculate efficiency for each contrast (`s3.Efficiency`)
  - Output: on terminal

```
Stimulus: stimA
h[ 0] norm. std. dev. = 0.1415
Stimulus: stimB
h[ 0] norm. std. dev. = 0.1301
Stimulus: stimC
h[ 0] norm. std. dev. = 0.1368
General Linear Test: GLT #1
LC[0] norm. std. dev. = 0.1677
General Linear Test: GLT #2
LC[0] norm. std. dev. = 0.1765
General Linear Test: GLT #3
LC[0] norm. std. dev. = 0.1680
```

Norm. Std. Dev.  
for 3 regressors

Norm. Std. Dev.  
for 3 contrasts

- Efficiency is a relative number!

## Experiment Design in AFNI

- Toy example: Design an experiment and check its efficiency
  - Try modeling with TENT functions (modifying `s3.Efficiency`): `TENT(0,12,7)`

```
Stimulus: stimA
h[ 0] norm. std. dev. = 0.1676
...
h[ 6] norm. std. dev. = 0.1704
Stimulus: stimB
h[ 0] norm. std. dev. = 0.1694
...
h[ 6] norm. std. dev. = 0.1692
Stimulus: stimC
h[ 0] norm. std. dev. = 0.1666
...
h[ 6] norm. std. dev. = 0.1674
General Linear Test: GLT #1
LC[0] norm. std. dev. = 0.5862 (0.1677)
General Linear Test: GLT #2
LC[0] norm. std. dev. = 0.5826 (0.1765)
General Linear Test: GLT #3
LC[0] norm. std. dev. = 0.5952 (0.1680)
```

Norm. Std. Dev.  
for 21 regressors

Norm. Std. Dev.  
for 3 contrasts

## Experiment Design in AFNI

- Design search: Find an efficient design
  - TR = 2s, 300 TR's, 3 stimulus types, 50 repetitions for each type
  - Script @DesignSearch: Parameters

```
# TOGGLE btw the following 2 model parameters
set model = GAM # toggle btw GAM and TENT
set eff = SUM # toggle btw SUM and MAX

# experiment parameters
set ts = 300 # length of timeseries
set stim = 3 # number of input stimuli
set num_on = 50 # time points per stimulus

# execution parameters
set iterations = 100 # number of iterations
set seed = 248390 # initial random seed
set outdir = Results # move output to this directory
set TR = 2 # TR Length in seconds
set ignore = 4 # number of TRs ignored
set show = 10 # number of designs shown

# Directories to store output files
set outdir = ${outdir}_${model}_seff
set LCfile = $outdir/LC
if ("${model}" == "TENT") set model = "${model}''(0,12,7)'
```

## Experiment Design in AFNI

- **Design search: Find an efficient design**

- Script @DesginSearch (continue): generate randomized designs

```
# make sure $outdir_exists
...
# compare many randomized designs
foreach iter (`count -digits 3 1 $iterations`)

    # make some other random seed
    @ seed = $seed + 1
    # create random order stim files

    RSFgen -nt ${ts} \
        -num_stimts ${stim} \
        -nreps 1 ${num_on} \
        -nreps 2 ${num_on} \
        -nreps 3 ${num_on} \
        -seed ${seed} \
        -prefix RSFstim${iter}. >& /dev/null
```

## Experiment Design in AFNI

- **Design search: Find an efficient design**

- Script @DesginSearch (continue): Convert stimulus coding into timing

```
make_stim_times.py -files RSFstim${iter}.1.1D RSFstim${iter}.2.1D \
    RSFstim${iter}.3.1D \
    -prefix stim${iter} \
    -nt 300 \
    -tr ${TR} \
    -nruns 1
```

## Experiment Design in AFNI

- **Design search: Find an efficient design**

- Script @DesginSearch (continue): run regression analysis

```
3dDeconvolve \
    -nodata ${ts} $TR \
    -nfirst $ignore \
    -nlast 299 \
    -polort 2 \
    -num_stimts ${stim} \
    -stim_times 1 "stim${iter}.01.1D" "$model" \
    -stim_label 1 "stimA" \
    -stim_times 2 "stim${iter}.02.1D" "$model" \
    -stim_label 2 "stimB" \
    -stim_times 3 "stim${iter}.03.1D" "$model" \
    -stim_label 3 "stimC" \
    -gltsym "SYM: stimA -stimB" \
    -gltsym "SYM: stimA -stimC" \
    -gltsym "SYM: stimB -stimC" \
    >& Eff${iter}
```

## Experiment Design in AFNI

- **Design search: Find an efficient design**

- Script @DesginSearch (continue): Calculate norm. std. dev. for the design

```
set nums = ( `awk -F= '/LC/ {print $2 * 100}' Eff${iter}` )
if ("${eff}" == "SUM") then
    # save the sum of the 3 normalized std dev
    set num_sum = `ccalc -eval "$nums[1] + $nums[2] + $nums[3]"`
    echo -n "$num_sum = $nums[1] + $nums[2] + $nums[3] : " >> $LCfile
    echo "iteration $iter, seed $seed" >> $LCfile
endif
if ("${eff}" == "MAX") then
    # get the max of the 3 normalized std dev
    set imax=`ccalc -form int -eval \
        "argmax($nums[1], $nums[2], $nums[3])"`
    set max = $nums[$imax]
    echo -n "$max = max($nums[1], $nums[2], $nums[3]) " >> $LCfile
    echo "iteration $iter, seed $seed" >> $LCfile
endif
```

## Experiment Design in AFNI

### • Design search: Find an efficient design`

#### o Script @DesginSearch (continue): Output

The most 10 efficient designs are (in descending order):

```
0.472800 = 0.1553 + 0.1596 + 0.1579 : iteration 092, seed 2483999
0.475300 = 0.1555 + 0.1610 + 0.1588 : iteration 043, seed 2483950
0.480300 = 0.1564 + 0.1632 + 0.1607 : iteration 020, seed 2483927
0.485600 = 0.1666 + 0.1560 + 0.1630 : iteration 006, seed 2483913
0.486800 = 0.1572 + 0.1615 + 0.1681 : iteration 044, seed 2483951
0.487200 = 0.1547 + 0.1663 + 0.1662 : iteration 100, seed 2484007
0.487400 = 0.1638 + 0.1626 + 0.1610 : iteration 059, seed 2483966
0.487700 = 0.1590 + 0.1605 + 0.1682 : iteration 013, seed 2483920
0.488700 = 0.1598 + 0.1659 + 0.1630 : iteration 060, seed 2483967
0.490500 = 0.1665 + 0.1635 + 0.1605 : iteration 095, seed 2484002
```

#### o Efficient design (under Results\_GAM\_SUM):

```
ldplot `ls Results_GAM_SUM/stim092.*.1D` &
```

## Experiment Design in AFNI

### • Design search: Find an efficient design

#### o Script @DesginSearch (continue): try other options

##### ▪ TENT functions and summing

```
set model = TENT
set eff = SUM
```

##### ▪ GAM and minimax

```
set model = GAM
set eff = MAX
```

##### ▪ TENT functions and minimax

```
set model = TENT
set eff = MAX
```

## Summary

- Useful bandwidth: 0.01 – 0.15 Hz
- Randomization
  - o 2 kinds: sequence and ISI
  - o Sequence randomization always good?
    - Experiment constraint
    - May not change efficiency much, but still good from other perspectives: Efficiency is not everything!
    - Neurological consideration that may not be considered through efficiency calculation
      - E.g., saturation, habituation, expectation, predictability, etc.
- Nothing is best in absolute sense
  - o Modeling approach: Pre-fixed HRF, basis function modeling, or else?
  - o Specific statistical tests
    - Efficient design for one test is not necessary ideal for another

## Miscellaneous

- Dealing with low frequencies
  - o Model drifting with polynomials (additive effect): 3dDeconvolve -polort
  - o High-pass filtering (additive effect): 3dFourier -highpass
  - o Global mean scaling (multiplicative or amplifying effect)
- Control condition
  - o Baseline rarely meaningful especially for higher cognitive regions
  - o If interest is on contrasts, null events are not absolutely necessary
  - o If no control exists
    - High-pass filtering (additive effect): 3dFourier -highpass
    - Scaling by and regressing out white matter or ventricular signal
- Multiple runs: concatenate or not
  - o Analyze each run separately
  - o Concatenate but analyze with separate regressors of an event across runs
  - o Concatenate but analyze with same regressor of an event across runs