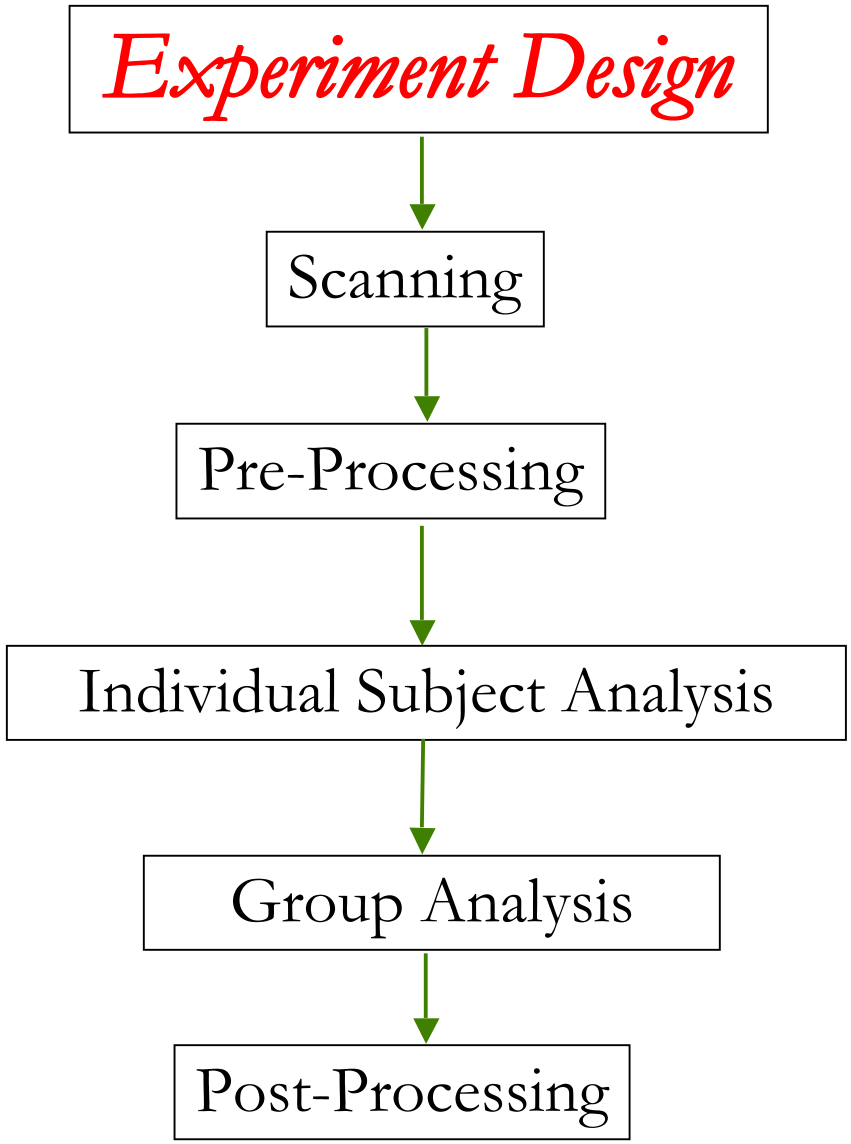
FMRI Analysis



Scheme of the Talk

- Design Types
  - Block
  - Event-related
  - Mixed
- Players in Experiment Design
- Intuitive Thinking in Frequency Domain
  - Usable frequency bandwidth for FMRI data
- Statistical Theory: how to arrange events/conditions/tasks?
  - Efficiency (power)
- Experiment Design in AFNI
  - **`RSFgen`** and **`3dDeconvolve`**
- Summary
- Miscellaneous

Design Types

- Event-related design
  - Modeling options
    - Rigid - Prefixed shape: `GAM(p,q)` (instantaneous duration), BLOCK(d,p)
      - Reliable and low cost if the HRF is very close to the model
    - Flexible - Whatever fits the data: deconvolution: **TENT**(b,c,n), CSPLIN(b,c,n)
      - Sensitive to HRF subtle changes across regions/conditions
      - High statistical cost; over-fitting; difficulty in group analysis
    - Middle ground - Various basis functions: **SPMG1**/2/3, **SIN, POLY**
- Block design
  - Conditions with lasting durations of more than one TR
  - Other terminologies: epoch, box-car
  - Usually modeled with prefixed-shape HRF (**BLOCK**), but
    - basis function (**TENT**) approach for flexible shapes
    - multiple events for each block: can model amplitude attenuation
- Mixed design

Power and Efficiency

- Two types of error in statistical inference
  - Type I
    - Reject null hypothesis when it's true
    - False positive, specificity
  - Type II
    - Reject alternative hypothesis when it's true
    - False negative, sensitivity
    - Power = 1 – type II error: success to detect BOLD response
- Efficiency
  - Relative measure of desirability of an estimator or experiment design
  - Proportional to power: higher efficient design more likely detects activations
  - Involves comparisons of potentially infinite possibilities/procedures
  - Our focus: comparison of different event sequences with all other parameters (# of conditions/time points) fixed

Players in Experiment Design

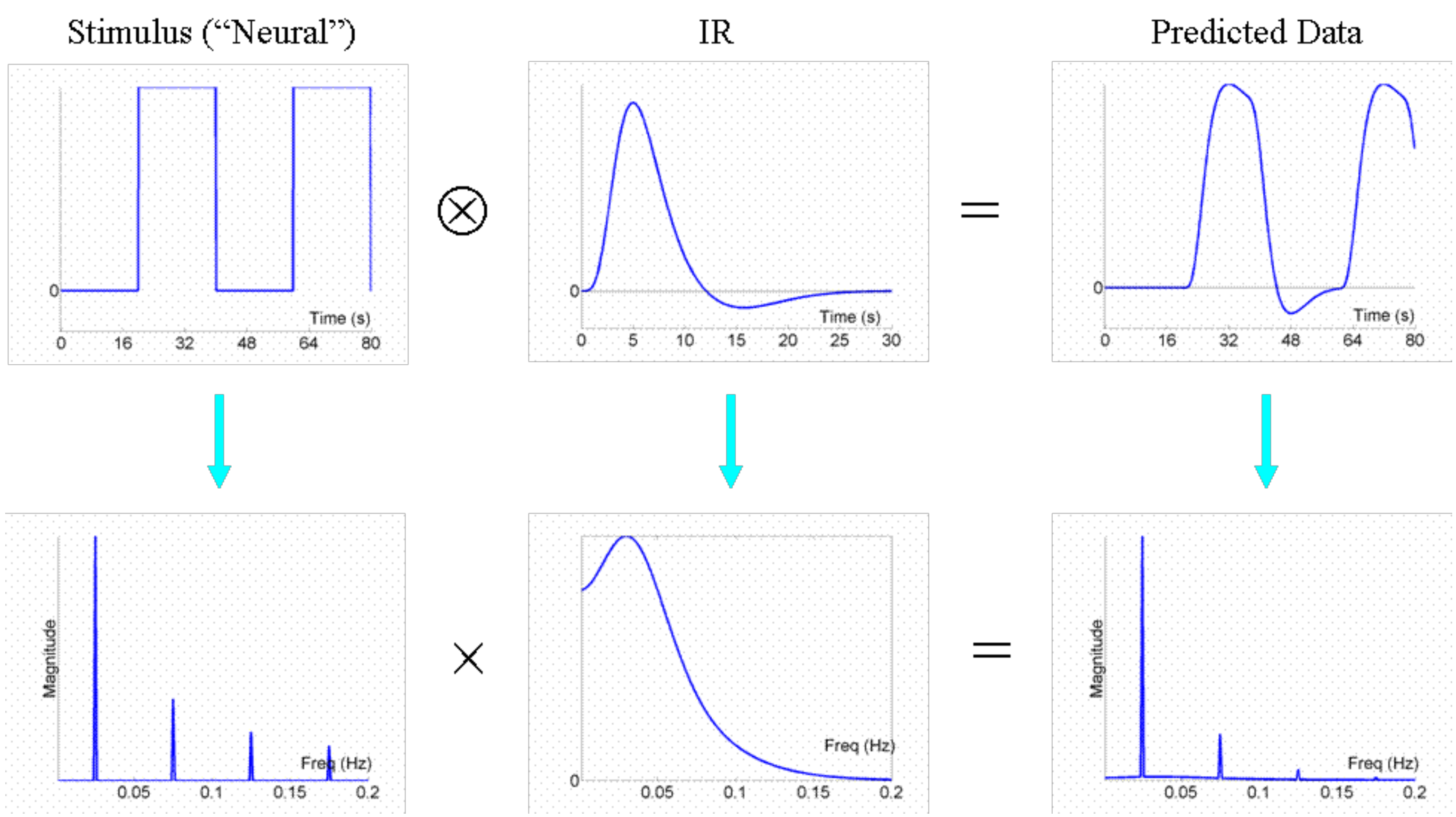
- Number of subjects (n)
  - Important for group analysis: inter-subject vs. intra-subject variation
  - Power (success to detect signal if present) roughly proportional to $\sqrt{n}$
  - Design type: block vs. event-related
  - Recommended: 20+ for event-related; Current practice: 12 – 20
- Number of time points
  - Important for individual subject analysis, but also affects group analysis implicitly
  - 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), but
  - Power improvement limited by weaker MR signal
  - Shorter TR → shorter ISI → higher event freq → higher correlation → less power
  - Usually limited by hardware considerations

Players in Experiment Design

- Design of the study
  - Complexity: factors, levels, covariate, contrasts of interest, …
  - Design choices may limit statistical analysis options
- Number of events per class (sample size for a regressor)
  - The more the better (20+), but no magic number
- Number of condition classes (regressors)
  - Limited by scanning time and confounded by low frequencies
- HRF modeling
  - Fixed shape, whatever fits the data, or other basis functions?
- **Event arrangement**
  - How to design? How to define the ‘best’ design?
  - Efficiency: achieve highest statistical power within fixed scanning time
- Inter-Stimulus Interval (ISI) and Stimulus Onset Asynchrony (SOA)
  - ISI: from the end (offset) of an event to the beginning (onset) of the next
  - SOA = stimulus duration + ISI

Intuitive Thinking

- Classical HRF
  - Convolution in time = multiplication in frequency
  - IRF plays a role of low-pass filter
  - Toy example: block design, 20s ON, and 20s OFF
  - Stimuli: fundamental frequency (*f* = 0.025) and its harmonics (3*f*, 5*f*, …)



Intuitive Thinking

- Event frequency
  - Optimal frequency: 0.03 Hz (period 30 s)
    - Implication for block designs: optimal duration – about 15s
  - Upper bound: 0.20 Hz (5s)
    - Submerged in the sea of white noise
    - Implication for event-related designs: average ISI > 5s
  - Lower bound: 0.01 Hz (100 s)
    - Confounded (highly correlated) with drift effect or removed by high-pass filtering
    - Implication for block designs: maximum duration about 50s*

      *Longer blocks could still be analyzed (see last slide)
  - Usable bandwidth: 0.01 – 0.20 Hz
    - Spread events within the frequency window
    - Varying frequencies allows us to catch various segments of the HRF

Statistical Theory

- Regression Model (GLM)
  - $Y = X\beta + \varepsilon$, X: design matrix with regressors as columns
- General Linear testing
  - Hypothesis H_0: $c'\beta = 0$ with c = vector $(c_0, c_1, \ldots, c_p)$ or matrix
    - **$t = c'\beta / \sqrt{[c'(X'X)^{-1}c\ MSE]}$** ($MSE$: unknown but same across tests)
      - Signal-to-noise ratio
      - Effect vs. uncertainty
    - $\sqrt{(c' (X'X)^{-1} c)}$: **normalized standard deviation** of contrast $c'b$
      - Scaling factor for uncertainty/unreliability/imprecision, and totally under our control
      - Efficiency = $1/\sqrt{[c'(X'X)^{-1}c]}$: Smaller norm. std. dev. → more efficient
      - $X'X$ measures co-variation among regressors: Less correlated regressors → more efficient and easier to tease apart regressors
    - Goal: find a design (X) that renders low norm. std. dev. or less correlated regressors
    - Assuming no temporal correlations in the residuals: real power might be slightly lower

Statistical Theory

- General Linear testing
  - Multiple tests:

    H_{01}: $c_1'\beta = 0$ with $c_1 = (c_{10}, c_{11}, \ldots, c_{1p})$, …

    H_{0k}: $c_k'\beta = 0$ with $c_k = (c_{k0}, c_{k1}, \ldots, c_{kp})$

    - Efficiency (sensitivity): a relative value; dimensionless
      - in AFNI: 1/∑individual norm. std dev.'s
      - ∑individual efficiencies in *optseq*
    - Efficiency is a relative measure
      - **Ordinal** meaning, but **no magnitude** sense (a design is 3X more efficient than another?)
      - We're interested only for an experiment with a specific parameter set and relevant linear tests
      - A design efficient for a contrast, but not necessarily true for each regressor *per se* or another contrast
      - Regressors correlated to some extent? Not necessarily a problem at all except for collinearity
    - Search for an efficient design
      - All parameters fixed; Only wiggle room: event sequence
      - Minimizing ∑individual norm. std dev.'s (obtain an overall optimum)
      - Minimax approach: Minimize the maximum of norm. std dev.'s (avoid the worst)

Experiment Design in AFNI

- Block experiments: manual design
- AFNI programs for designing event-related experiments
  - **RSFgen**: design X by generating randomized events; use **make_random_timing.py** if events are NOT synchronized/locked with TR
  - **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 the same type every 6 TR's
    - ISI = 12 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 (**GAM**) or deconvolution (**TENT**)?
  - Go to directory **AFNI_data3/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
    - `1dplot 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`**
  - Check the statistics of stimulus timing (**s2.StimStat**)
    - **`timing_tool.py -multi_timing stim.01.1D stim.02.1D stim.03.1D\`**

      `-run_len 600 -multi_stim_dur 0.5 -multi_show_isi_stats`

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_stimts 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 of interest

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
  - With TENT functions (modifying **s3.Efficiency**): TENT(0,12,7) (less efficient)

```
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: AUC or individual basis function (stim[[0..6]])?

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 time series
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}_$eff
set LCfile       = $outdir/LC
if ("$model" == "TENT") set model = ${model}'(0,12,7)'
```

Experiment Design in AFNI

- **Design search: Find an efficient design**
  - Script `@DesignSearch` (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 `@DesignSearch` (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 @DesignSearch (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 @DesignSearch (continue): Calculate norm. std. dev. for the design

```
set nums = ( `awk -F= '/LC/ {print $2}' Eff${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`**
  - Run the script tcsh @DesginSearch: 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

  - Efficient design (under Results_GAM_SUM):

    1dplot Results_GAM_SUM/RSFstim092.*.1D &

    Stimulus timing files are Results_GAM_SUM/stim092.*.1D

Experiment Design in AFNI

- **Design search: Find an efficient design**
  - Script @DesignSearch (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

Find an efficient design

- Efficient design search works only for event-related type
- Block or mixed type is typically designed manually
- Most parameters (TR, number of subjects/conditions/runs/sessions/time points, …) are preset usually through other considerations before design search
- Not really an optimization process
  - Infinite possibilities
  - Used to avoid undesirable designs (collinearity problem) more than optimal one(s)
  - A manual design might be approximately (if not equally) optimal

Summary

- Useful bandwidth: 0.01 – 0.2 Hz
  - Optimal frequency: around 0.03 Hz
- Randomization
  - Two kinds: sequence and ISI
  - Sequence randomization always good?
    - Experiment constraint
    - May not change efficiency much, but still good from other perspectives: Efficiency is not everything!
    - Neurological consideration not considered through efficiency calculation
      - E.g., saturation, habituation, expectation, predictability, etc.
- Nothing is best in absolute sense
  - Modeling approach: Pre-fixed HRF, basis function modeling, or else?
  - Specific tests: Efficient design for one test is not necessarily ideal for another
- Use to design an efficient experiment
  - Works with constraints of an event-related experiment set by the user
  - Doesn't work with block/mixed designs

Miscellaneous

- Dealing with low frequencies
  - Model drifting with polynomials (**additive** effect): **`3dDeconvolve -polort`**
    - One order per 150s (with a cutoff ~0.003Hz): blocks of 150s or longer won't be detectable
    - Or compare different drifting models
  - Usually not recommended - High-pass filtering (**additive** effect): **`3dFourier -highpass`**
  - Global mean scaling (**multiplicative** or modulating effect)
- Control condition
  - Baseline rarely meaningful especially for higher cognitive regions
  - Keep the subject as busy as possible?
  - If interest is on contrasts, null events are not absolutely necessary
  - If no control exists
    - High-pass filtering (additive effect): **3dFourier –highpass**
    - Scaling by or regressing out global mean, white matter or ventricular signal
- Multiple runs: concatenate or not
  - Analyze each run separately: enough time points per run
  - Concatenate but analyze with separate regressors of an event type across runs: test for habituation
  - Concatenate but analyze with same regressor of an event type across runs (default in AFNI)