HowTo 03: stimulus timing design (hands-on)

- Goal: to design an effective random stimulus presentation
  - → end result will be stimulus timing files
  - → example: using an event related design, with simple regression to analyze

- Steps:
  0. given: experimental parameters (stimuli, # presentations, # TRs, etc.)
  1. create random stimulus functions (one for each stimulus type)
  2. create ideal reference functions (for each stimulus type)
  3. evaluate the stimulus timing design

- Step 0: the (made-up) parameters from HowTo 03 are:
  - → 3 stimulus types (the classic experiment: "houses, faces and donuts")
  - → presentation order is randomized
  - → TR = 1 sec, total number of TRs = 300
  - → number of presentations for each stimulus type = 50 (leaving 150 for fixation)
    - fixation time should be 30% ~ 50% total scanning time
  - → 3 contrasts of interest: each pair-wise comparison
  - → refer to directory: **`AFNI_data1/ht03`**

- Step 1: creation of random stimulus functions

  → RSFgen : Random Stimulus Function generator

  → command file: **`c01.RSFgen`**

```
RSFgen -nt 300 -num_stimts 3                  \
       -nreps 1 50 -nreps 2 50 -nreps 3 50    \
       -seed 1234568 -prefix RSF.stim.001.
```

  → This creates 3 stimulus timing files:

```
RSF.stim.001.1.1D  RSF.stim.001.2.1D  RSF.stim.001.3.1D
```

- Step 2: create ideal response functions (linear regression case)

  → waver: creates waveforms from stimulus timing files

    - effectively doing convolution

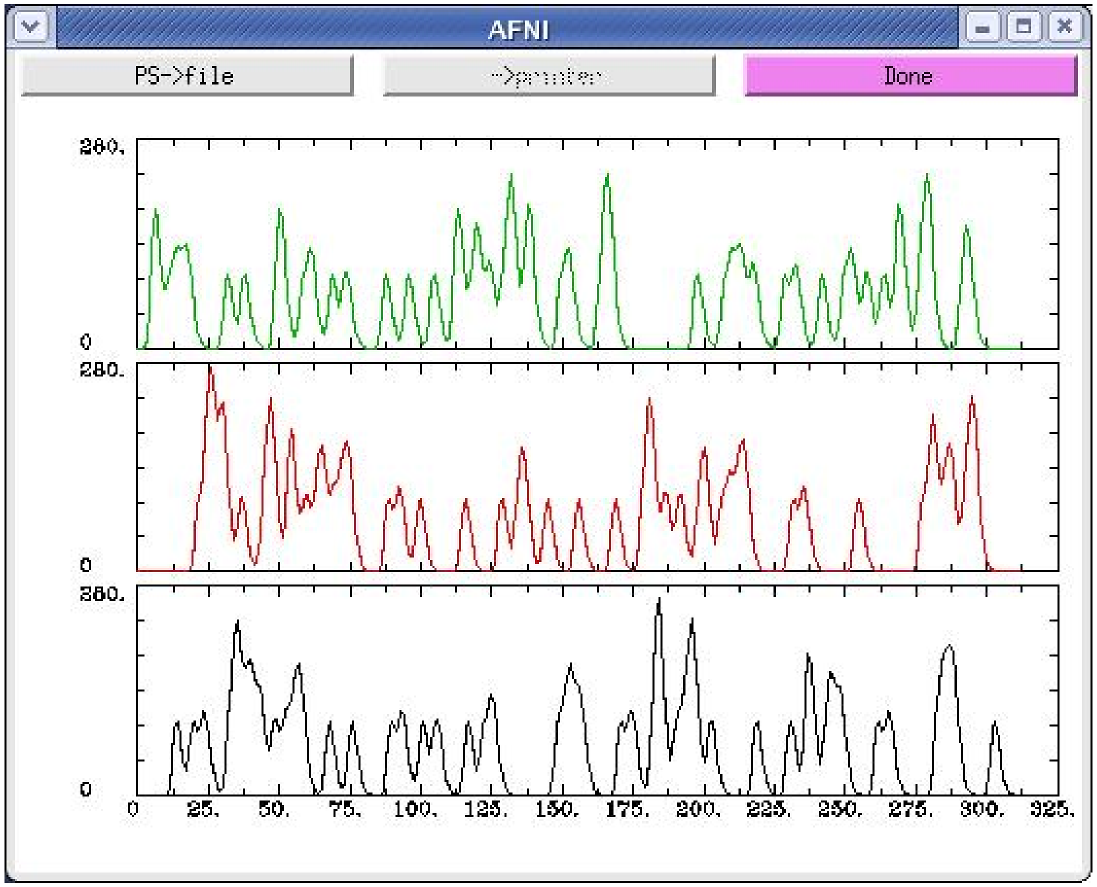
  → command file: **`c02.waver`**

```
waver -GAM -dt 1.0 -input RSF.stim.001.1.1D
```

  → this will output (to the terminal window) the ideal response function, by convolving the Gamma variate function with the stimulus timing function

  → output length allows for stimulus at last TR (= 300 + 13, in this example)

  → use '1dplot' to view these results, command: **`1dplot wav.*.1D`**



- the first curve (for **`wav.hrf.001.1.1D`**) is displayed on the bottom
- x-axis covers 313 seconds, but the graph is extended to a more "round" 325
- y-axis happens to reach 274.5, shortly after 3 consecutive type-2 stimuli
- the peak value for a single curve can be set using the **`-peak`** option in **`waver`**

  → **`default peak is 100`**

- it is worth noting that there are no duplicate curves
- can also use **`'waver -one'`** to put the curves on top of each other

- Step 3: evaluate the stimulus timing design
  - → use '3dDeconvolve -nodata': experimental design evaluation
  - → command file: **`c03.3dDeconvolve`**
  - → command:

```
3dDeconvolve -nodata                               \
    -nfirst 4 -nlast 299 -polort 1                 \
    -num_stimts 3                                  \
    -stim_file 1 "wav.hrf.001.1.1D"                \
    -stim_label 1 "stim_A"                         \
    -stim_file 2 "wav.hrf.001.2.1D"                \
    -stim_label 2 "stim_B"                         \
    -stim_file 3 "wav.hrf.001.3.1D"                \
    -stim_label 3 "stim_C"                         \
    -glt 1 contrasts/contrast_AB                   \
    -glt 1 contrasts/contrast_AC                   \
    -glt 1 contrasts/contrast_BC
```

- Use the 3dDeconvolve output to evaluate the normalized standard deviations of the contrasts.
- For this HowTo script, the deviations of the GLT's are summed. Other options are valid, such as summing all values, or just those for the stimuli, or summing squares.
- Output (partial):

```
Stimulus: stim_A
  h[ 0] norm. std. dev. =   0.0010
Stimulus: stim_B
  h[ 0] norm. std. dev. =   0.0009
Stimulus: stim_C
  h[ 0] norm. std. dev. =   0.0011
General Linear Test: GLT #1
  LC[0] norm. std. dev. =   0.0013
General Linear Test: GLT #2
  LC[0] norm. std. dev. =   0.0012
General Linear Test: GLT #3
  LC[0] norm. std. dev. =   0.0013
```

- What does this output mean?

  → What is **`norm. std. dev.`**?

  → How does this compare to results using different stimulus timing patterns?

Basics about Regression

- Regression Model (General Linear System)
  - → Simple Regression Model (one regressor): $Y(t) = \alpha_0+\alpha_1 t+\beta\, r(t)+\varepsilon(t)$
    - Run **`3dDeconvolve`** with regressor *r(t)*, a time series IRF
  - → Deconvolution and Regression Model (one stimulus with a lag of *p* TR's):

    $Y(t) = \alpha_0+\alpha_1 t+\beta_0 f(t)+\beta_1 f(t-TR)\ldots+\beta_p f(t-p{*}TR)+\varepsilon(t)$
    - Run **`3dDeconvolve`** with stimulus files (containing 0's and 1's)
- Model in Matrix Format: $Y = X\beta + \varepsilon$
  - → X: design matrix - more rows (TR's) than columns (baseline parameters + beta weights).

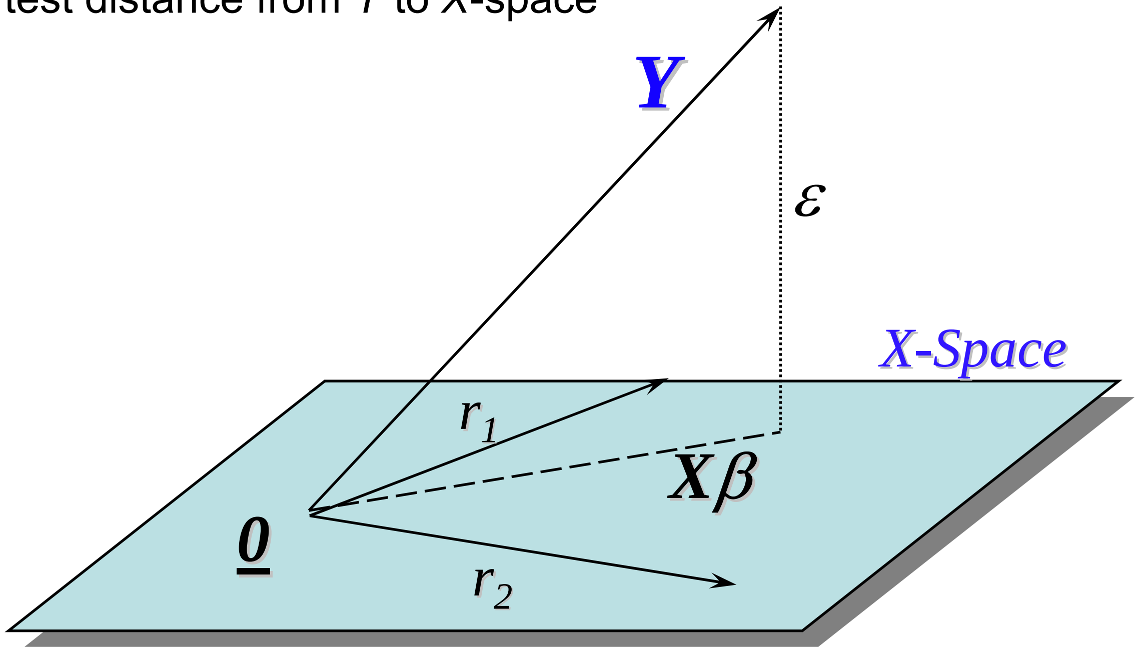
$$\begin{array}{ccc}
\alpha_0 & \alpha_1 & \beta \\
\hline
1 & 1 & r(0) \\
1 & 2 & r(1) \\
 & . \; . \; . & \\
1 & N\text{-}1 & r(N\text{-}1)
\end{array}
\qquad\qquad
\begin{array}{ccccc}
\alpha_0 & \alpha_1 & \beta_0 & \ldots & \beta_p \\
\hline
1 & p & f_p & \ldots & f_0 \\
1 & p+1 & f_{p+1} & \ldots & f_1 \\
 & . \; . \; . & & & \\
1 & N\text{-}1 & f_{N-1} & \ldots & f_{N-p-1}
\end{array}$$

  - → ε: random (system) error $N(0, \sigma^2)$

- X matrix examples (based on modified HowTo 03 script, stimulus #3):
  - → regression: baseline, linear drift, 1 regressor (ideal response function)
  - → deconvolution: baseline, linear drift, 5 regressors (lags)

regression			deconvolution - with lags (3-7)						
1	0	0	1	0	0	0	0	0	0
1	1	0	1	1	0	0	0	0	0
1	2	0.14	1	2	0	0	0	0	0
1	3	9.11	1	3	0	0	0	0	0
1	4	56.05	1	4	1	0	0	0	0
1	5	136.9	1	5	1	1	0	0	0
1	6	188.2	1	6	0	1	1	0	0
1	7	174.2	1	7	0	0	1	1	0
1	8	121.9	1	8	0	0	0	1	1
1	9	78.1	1	9	0	0	0	0	1
1	10	80.63	1	10	1	0	0	0	0
1	11	104.4	1	11	0	1	0	0	0
1	12	112.9	1	12	0	0	1	0	0
1	13	124.9	1	13	1	0	0	1	0
1	14	136.4	1	14	0	1	0	0	1
1	15	130.6	1	15	0	0	1	0	0
1	16	133.2	1	16	1	0	0	1	0
1	17	139.8	1	17	0	1	0	0	1

- Solving the Linear System : $Y = X\beta + \varepsilon$
  - → the basic goal of `3dDeconvolve`
  - → Least Square Estimate (LSE): making sum of squares of residual (unknown/unexplained) error $\varepsilon'\varepsilon$ minimal → Normal equation: $(X'X)\,\beta = X'Y$
  - → When X is of full rank (all columns are independent), $\hat{\beta} = (X'X)^{-1}X'Y$
- Geometric Interpretation:
  - → project vector Y onto a space spanned by the regressors (the column vectors of design matrix X)
  - → find shortest distance from Y to X-space



- <u>Multicollinearity Problem</u>
  - → **`3dDeconvolve Error: Improper X matrix (cannot invert X'X)`**
  - → *X'X* is singular (not invertible) ↔ at least one column of *X* is linearly dependent on the other columns
  - → normal equation has no unique solution
  - → Simple regression case:
    - mistakenly provided at least two identical regressor files, or some inclusive regressors, in **`3dDeconvolve`**
    - all regressiors have to be orthogonal (exclusive) with each other
    - easy to fix: use **`1dplot`** to diagnose
  - → Deconvolution case:
    - mistakenly provided at least two identical stimulus files, or some inclusive stimuli, in **`3dDeconvolve`**
      - ➢ easy to fix: use **`1dplot`** to diagnose
    - intrinsic problem of experiment design: lack of randomness in the stimuli
      - ➢ varying number of lags may or may not help.
      - ➢ running RSFgen can help to avoid this
  - → see **`AFNI_data1/ht03/bad_stim/c20.bad_stim`**

- Design analysis
  - → $X'X$ invertible but $cond(X'X)$ is huge → linear system is sensitive → difficult to obtain accurate estimates of regressor weights
  - → Condition number: a measure of system's sensitivity to numerical computation
    - $cond(M)$ = ratio of maximum to minimum eigenvalues of matrix M
    - note, **`3dDeconvolve`** can generate both X and $(X'X)^{-1}$, but not $cond()$
  - → Covariance matrix estimate of regressor coefficients vector β:
    - $s^2(\beta) = (X'X)^{-1} MSE$
    - t test for a contrast $c'\beta$ (including regressor coefficient):
      - ➢ $t = c'\beta / \text{sqrt}(c' (X'X)^{-1} c \; MSE)$
      - ➢ contrast for condition A only: c = [0 0 1 0 0]
      - ➢ contrast between conditions A and B: c = [0 0 1 -1 0]
      - ➢ $\text{sqrt}(c' (X'X)^{-1} c)$ in the denominator of the t test indicates the relative stability and statistical power of the experiment design
    - $\text{sqrt}(c' (X'X)^{-1} c)$ = normalized standard deviation of a contrast $c'\beta$ (including regressor weight) → *these values are output by* **`3dDeconvolve`**
    - smaller $\text{sqrt}(c' (X'X)^{-1} c)$ → stronger statistical power in t test, and less sensitivity in solving the normal equation of the general linear system
    - RSFgen helps find out a good design with relative small $\text{sqrt}(c' (X'X)^{-1} c)$

- A bad example: see directory **`AFNI_data1/ht03/bad_stim/c20.bad_stim`**
  → 2 stimuli, 2 lags each
  → stimulus 2 happens to follow stimulus 1

baseline	linear drift	S1 L1	S1 L2	S2 L1	S2 L2
1	0	0	0	0	0
1	1	0	0	0	0
1	2	0	0	0	0
1	3	1	0	0	0
1	4	0	1	1	0
1	5	0	0	0	1
1	6	1	0	0	0
1	7	0	1	1	0
1	8	0	0	0	1
1	9	0	0	0	0
1	10	1	0	0	0
1	11	0	1	1	0
1	12	1	0	0	1
1	13	1	1	1	0
1	14	0	1	1	1
1	15	1	0	0	1
1	16	0	1	1	0
1	17	1	0	0	1
1	18	0	1	1	0
1	19	0	0	0	1

- So are these results good?

```
stim A:  h[ 0] norm. std. dev. =   0.0010
stim B:  h[ 0] norm. std. dev. =   0.0009
stim C:  h[ 0] norm. std. dev. =   0.0011
GLT #1:  LC[0] norm. std. dev. =   0.0013
GLT #2:  LC[0] norm. std. dev. =   0.0012
GLT #3:  LC[0] norm. std. dev. =   0.0013
```

- And repeat… see the script: **`AFNI_data1/ht03/@stim_analyze`**
  - → review the script details:
    - 100 iterations, incrementing random seed, storing results in separate files
    - only the random number seed changes over the iterations
  - → execute the script via command: **`./@stim_analyze`**
  - → "best" result: iteration 039 gives the minimum sum of the 3 GLTs, among all 100 random designs (see file **`stim_results/LC_sums`**)
  - → the **`3dDeconvolve`** output is in **`stim_results/3dD.nodata.039`**
- Recall the Goal: to design an effective random stimulus presentation (while preserving statistical power)
  - → Solution: the files **`stim_results/RSF.stim.039.*.1D`**

```
RSF.stim.039.1.1D  RSF.stim.039.2.1D  RSF.stim.039.3.1D
```