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`**

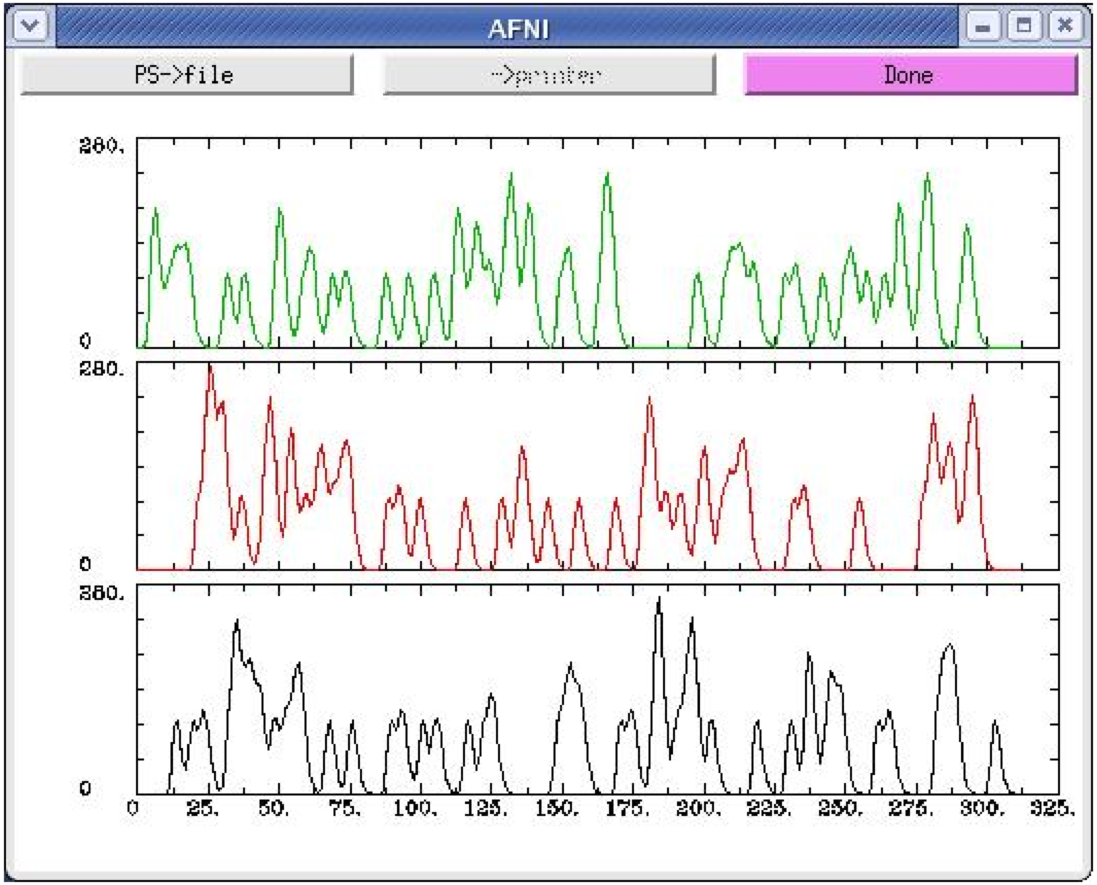
```
RSFgen -nt 300 -num_stimts 3                        \
       -nreps 1 50 -nreps 2 50 -nreps 3 50     \
       -seed 1234568 -prefix RSF.stim.001.
```

  - → 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):

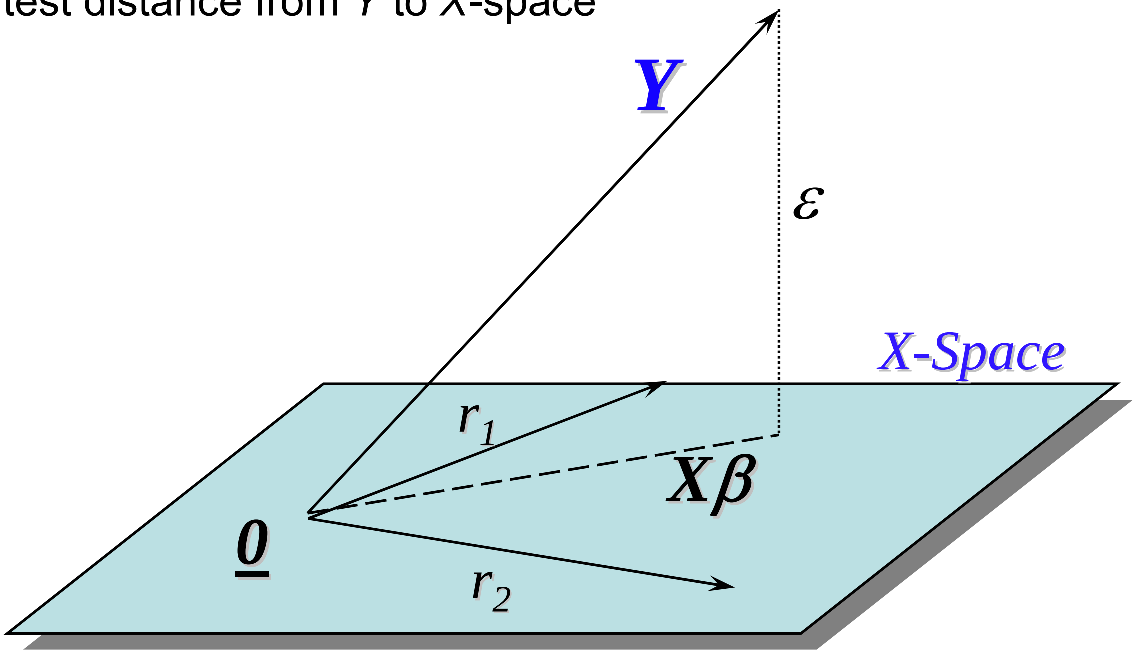
    $Y(t) = \alpha_0+\alpha_1 t+\beta_0 f(t)+\beta_1 f(t\text{-}TR)\ldots+\beta_p f(t\text{-}p{*}TR)+\varepsilon(t)$
    - Run **`3dDeconvolve`** with stimulus files (containing 0's and 1's)
- Model in Matrix Format: $Y = X\beta + \varepsilon$
  - → *X*: design matrix - more rows (TR's) than columns (baseline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

α_0	α_1	β
1	1	$r(0)$
1	2	$r(1)$
.	.	.
1	N-1	$r(N\text{-}1)$

α_0	α_1	β_0	...	β_p
1	p	f_p	...	f_0
1	p+1	f_{p+1}	…	f_1
.	.	.		
1	N-1	$f_{N\text{-}1}$	…	$f_{N\text{-}p\text{-}1}$

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

- 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



- X matrix examples (very simple - 4 stimulus events, data is perfectly modeled)
  - → suppose that we expect the response to a stimulus to look like (0, 2, 1, 0, 0, 0, …)
  - → regression: solve ***Y*** = $\beta 0$ * r0 + $\beta 1$ * r1 (for $\beta 0$ and $\beta 1$)
  - → deconvolution: solve ***Y*** = $\gamma 0$ * d0 + $\gamma 1$ * d1 + $\gamma 2$ * d2 + $\gamma 3$ * d3 (for $\gamma 0, \gamma 1, \gamma 2, \gamma 3$)

	expected		**regression**			**deconvolution**			
	response	***Y***	$\beta 0$	$\beta 1$		$\gamma 0$	$\gamma 1$	$\gamma 2$	$\gamma 3$
			r0	**r1**		**d0**	**d1**	**d2**	**d3**
stim	0	10	1	0		1	1	0	0
	2	14	1	2		1	0	1	0
	1	12	1	1		1	0	0	1
		10	1	0		1	0	0	0
stim	0	10	1	0		1	1	0	0
	2	14	1	2		1	0	1	0
	1	12	1	1		1	0	0	1
stim	0	10	1	0		1	1	0	0
stim	2 0	14	1	2		1	1	1	0
	1 2	16	1	3		1	0	1	1
	1	12	1	1		1	0	0	1
		10	1	0		1	0	0	0

- X matrix examples (based on modified HowTo 03 script, stimulus #3):
  - → regression: baseline, linear drift, 1 regressor (ideal response function)
  - → deconvolution: baseline, linear drift, 8 regressors (lags)
  - → decide on appropriate values of: α_0 α_1 β_i

Y	regression α_0	regression α_1	regression β_0	deconvolution - with lags (0-7) α_0	α_1	β_0	β_1	β_2	β_3	β_4	β_5	β_6	β_7
500	1	0	0	1	0	0	0	0	0	0	0	0	0
500	1	1	0	1	1	1	0	0	0	0	0	0	0
500.01	1	2	0.1	1	2	1	1	0	0	0	0	0	0
500.91	1	3	9.1	1	3	0	1	1	0	0	0	0	0
505.60	1	4	56.0	1	4	0	0	1	1	0	0	0	0
513.69	1	5	136.9	1	5	0	0	0	1	1	0	0	0
518.82	1	6	188.2	1	6	0	0	0	0	1	1	0	0
517.42	1	7	174.2	1	7	1	0	0	0	0	1	1	0
512.19	1	8	121.9	1	8	0	1	0	0	0	0	1	1
507.81	1	9	78.1	1	9	0	0	1	0	0	0	0	1
508.06	1	10	80.6	1	10	1	0	0	1	0	0	0	0
510.44	1	11	104.4	1	11	0	1	0	0	1	0	0	0
511.29	1	12	112.9	1	12	0	0	1	0	0	1	0	0
512.49	1	13	124.9	1	13	1	0	0	1	0	0	1	0
513.64	1	14	136.4	1	14	0	1	0	0	1	0	0	1
513.06	1	15	130.6	1	15	0	0	1	0	0	1	0	0
513.32	1	16	133.2	1	16	0	0	0	1	0	0	1	0
513.98	1	17	139.8	1	17	0	0	0	0	1	0	0	1

- 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

- <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):
      - $t = c'\beta / \mathrm{sqrt}(c' (X'X)^{-1} c\ MSE)$
      - contrast for condition A only: c = [0 0 1 0 0]
      - contrast between conditions A and B: c = [0 0 1 -1 0]
      - sqrt($c' (X'X)^{-1} c$) in the denominator of the t test indicates the relative stability and statistical power of the experiment design
    - sqrt($c' (X'X)^{-1} c$) = normalized standard deviation of a contrast $c'\beta$ (including regressor weight) → *these values are output by* **`3dDeconvolve`**
    - smaller 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 sqrt($c' (X'X)^{-1} c$)

- 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.039.3.1D13`