FMRI Data Analysis at Individual Level

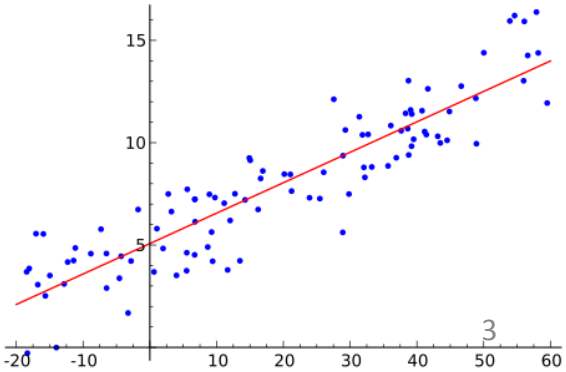
SSCC/NIMH/NIH/HHS

Overview

- Basics of linear model
- FMRI experiment types
  - Block design; Event related experiment; Mixed
- FMRI data decomposition: three components
  - Baseline + slow drift + effects of no interest; Effects of interest; Unknown
  - Effects of interest - understanding BOLD vs. stimulus: IRF
- Three modeling strategies
  - Fixed-shape IRF
  - No assumption about IRF shape
  - One major IRF plus shape adjustment
- Other issues
  - Multicollinearity
  - Catenation
  - Percent signal change

Basics of Linear Model

- Regression: relationship between a response/outcome (dependent) variable and one or more explanatory (independent) variables (regressors)
  - Simple regression: fit data with a straight line: Sir Francis Galton's original meaning: regression to mean
    - When 2 variables are not perfectly correlated, regression to mean exists
    - May show up in psychology (Daniel Kahneman): Rewards for good performance vs. punishment of mistakes (correlation vs. causation)
    - Lost in most cases including FMRI
  - Some statisticians just call it linear model
- Mathematical crystallization
  - $y_i = \alpha + \beta x_i + \varepsilon_i$, or $y_i = \alpha + \beta_1 x_{1i} + \ldots + \beta_k x_{ki} + \varepsilon_i$
  - $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}, \mathbf{X} = [1, x_1, x_2, \ldots, x_k]$
  - Assumption
    - linearity
    - white noise (independence) and Gaussianity $\boldsymbol{\varepsilon} \sim N(0, \sigma^2\mathbf{I})$



Basics of Linear Model

- Solution for linear regression $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$
  - Project data **y** onto the space of explanatory variables (**X**)
  - OLS $\hat{\beta} = (X^T X)^{-1} X^T y$
- Meaning of coefficient: β value, slope, marginal effect or effect size associated with a regressor
- Various statistical tests
  - Student *t*-test for each β (H_0: $\beta_3 = 0$)
  - Student *t*-test for linear combination of β values - general linear test (GLT), *e.g.*, H_0: $\beta_3 - \beta_5 = 0$, or H_0: $0.5*(\beta_3 + \beta_4) - \beta_5 = 0$
  - *F*-test for composite null hypothesis, *e.g.*, H_0: $\beta_3 = \beta_4 = \beta_5$ or H_0: $\beta_3 = \beta_4 = \beta_5 = 0$
  - Omnibus or overall *F*-test for the **whole** model, *e.g*, H_0: all β values are 0, or H_0: all β values of interest are 0

Linear Model with FMRI

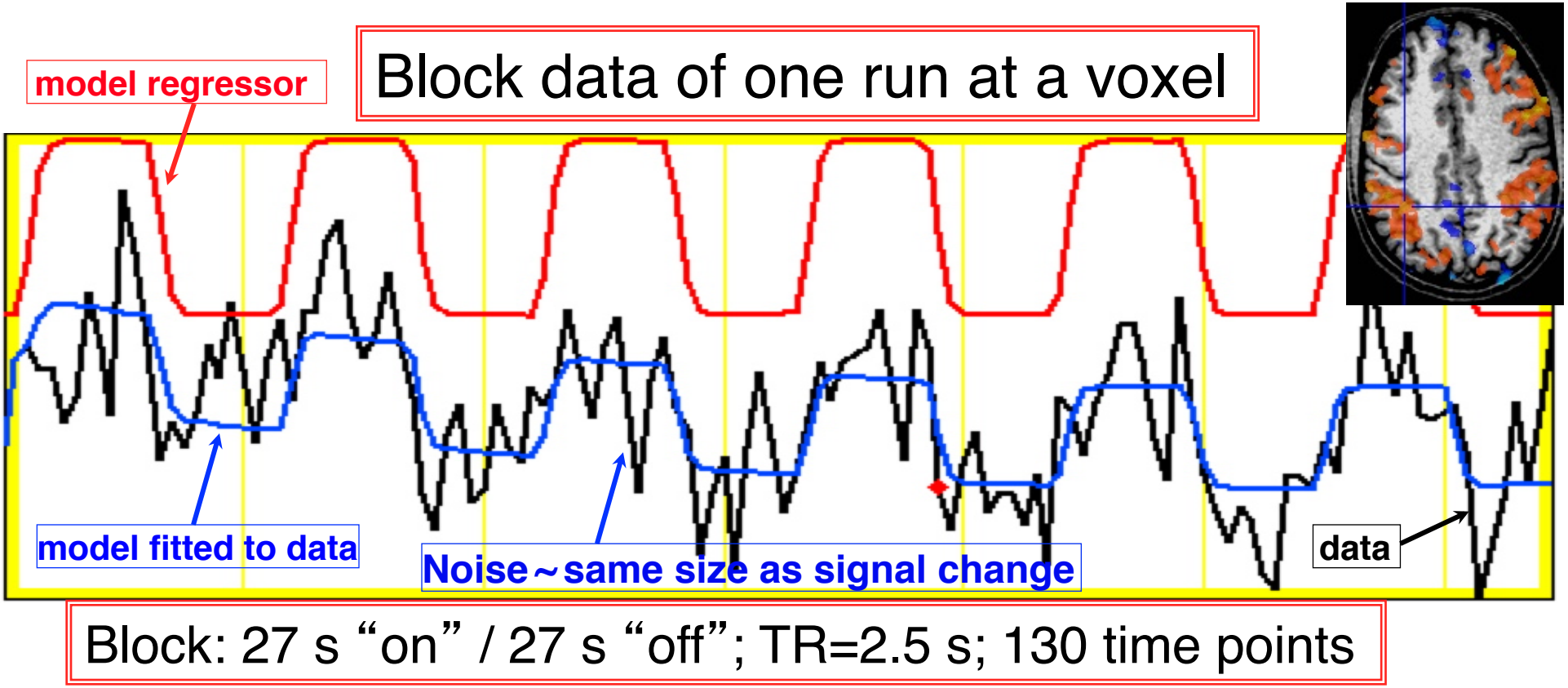
- Time series regression: data **y** is time series
  - Regressors: idealized response or yardstick
    - We get what we're looking for
    - It may miss something when we fail to recognize it
    - Regressor construction is quite challenging
  - Special handling: noise not white $\boldsymbol{\varepsilon} \sim N(0, \sigma^2 \boldsymbol{\Sigma})$ with temporal or serial correlation
    - Banded variance-covariance matrix $\boldsymbol{\Sigma}$
  - AKA general linear model (GLM) in other FMRI packages
    - General vs. generalized
- Same model for all voxels in the brain
  - Simultaneously solve the models: voxel-wise analysis, massively univariate method

FMRI Experiment Terminology

- Experiment setup
  - Number of subjects
  - Number of conditions (tasks, stimulus (trial, event) types): Factorial design?
  - Sample size (repetitions) per condition
  - Block, event-related, or mixed?
  - Inter-stimulus interval (ISI)
- Scanning parameters: TR, voxel size, data points (volumes), slice sequence (sequential or interleaved), slice thickness, removing first few TRs
- Scanning terms
  - Run: continuous scanning; a brief break before next run
  - Session: subjects come back after along period of time
  - Experiment or study

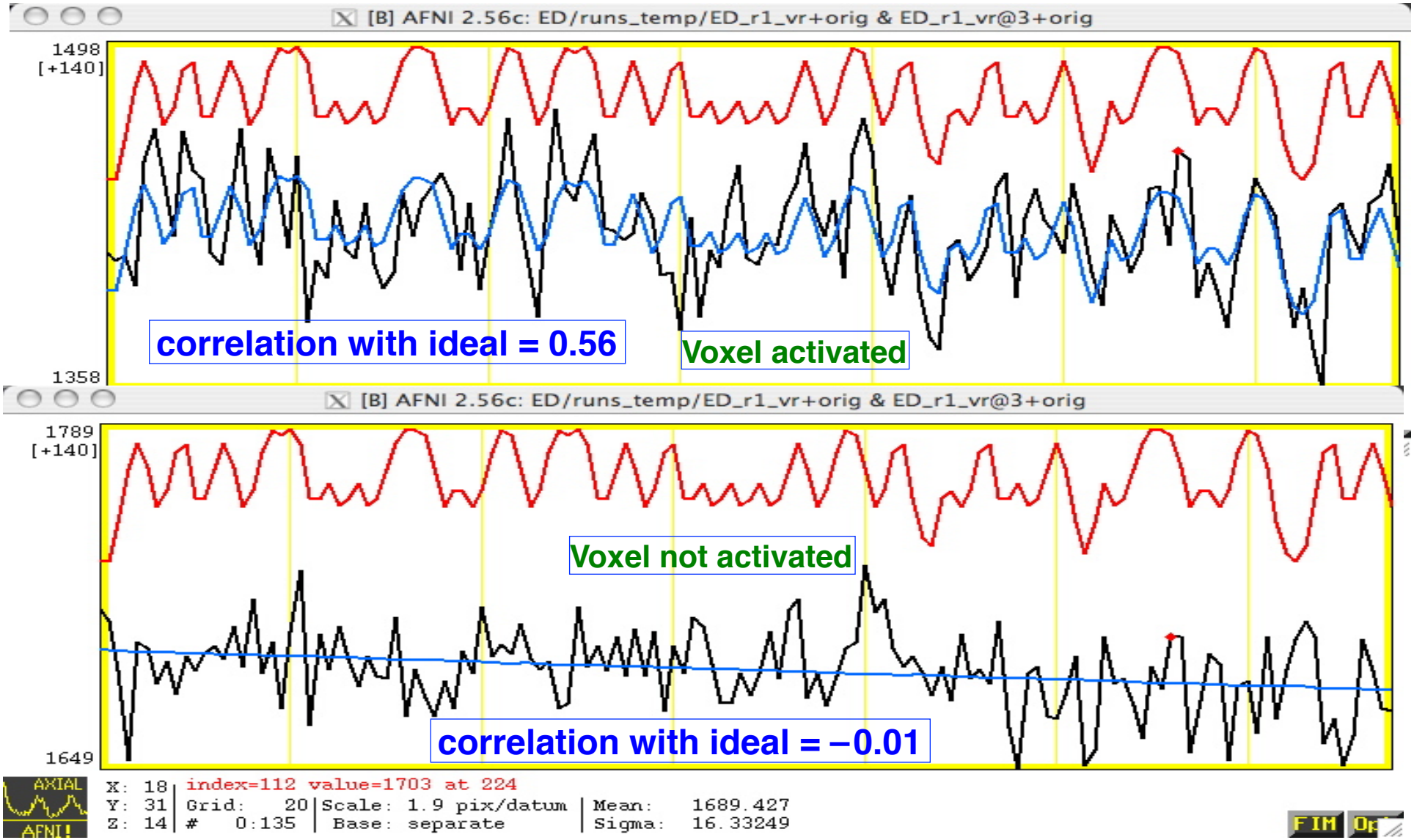
Types of FMRI Experiments

- Two classical types of experiment design
  - Block (boxcar) design
    - Each block lasts for more than one TR (e.g., 4 to 20s)
    - Each block is under one condition (e.g., watch a video clip), or a series of multiple trials (e.g., 10 consecutive blur images)
    - BOLD response is often visible in time series
    - SNR: noise magnitude about same as BOLD response
  - Event-related design
    - Each event or trial lasts for one TR or shorter
    - Events are randomly spaced and/or sequenced in time
    - BOLD response to stimulus tends to be weaker, since fewer nearby-in-time "activations" have overlapping signal changes
    - SNR: data looks more like noise (to the pitiful human eye)
- Mixed designs
  - Containing both events and blocks, *e.g.*, cue + video watching



- This is best voxel; most voxels are not fitted as good as this
- Activation amplitude and shape vary across blocks
  - Subject attention variability
  - Habituation (or attenuation): psychological/physiological level
  - Linearity assumption
  - Pure random effects

Event-Related Data at 2 Voxels



Lesson: ER-FMRI activation is not obvious via casual inspection

FMRI Data

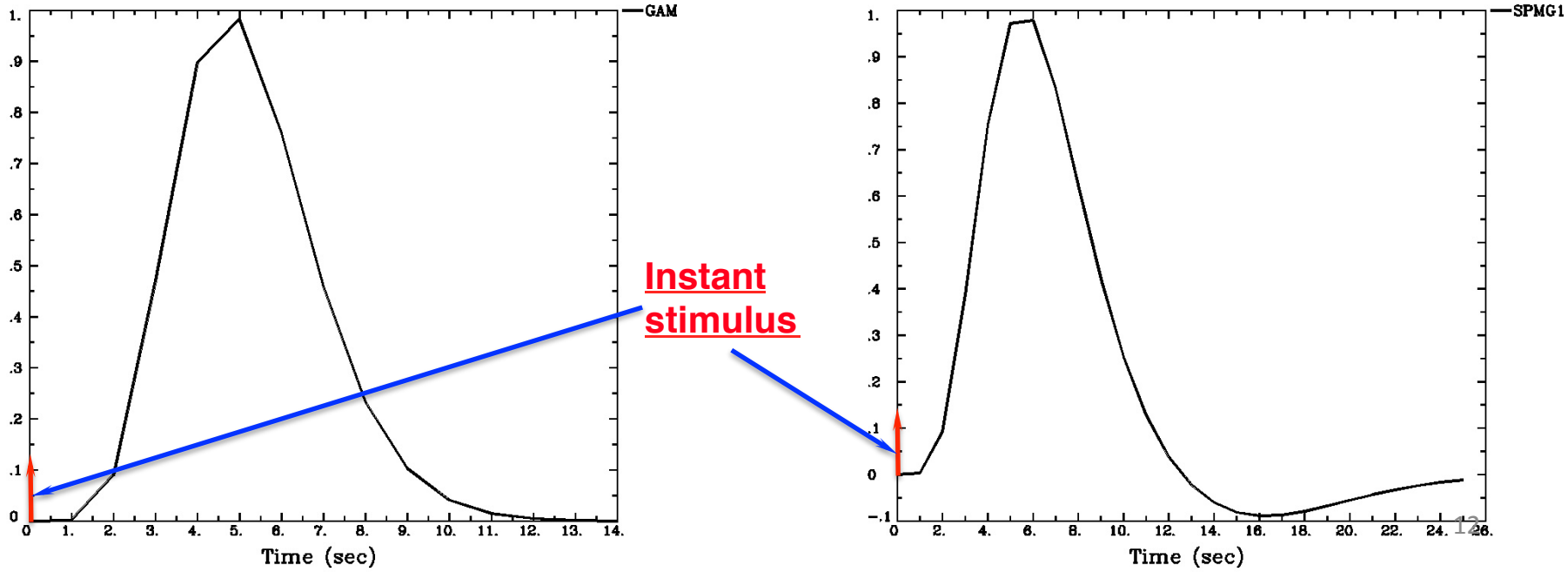
- Data partition: **Data = Signal + Noise**
  - **Data** = acquisition from scanner (voxel-wise time series)
    - What we have
  - **Signal** = BOLD response to stimulus; effects of interest + no interest
    - We don't really know the real signal!!!
    - Look for idealized components, or search for signal via repeated trials
    - Of interest: effect size (response amplitude) for each condition: beta
    - Of no interest: baseline, slow drift, head motion effects, …
  - **Noise** = components in data that interfere with signal
    - Practically the part we have don't know and/or we don't care about; that is, noise is the part we can't explain in the model
    - Will have to make some assumptions about its distribution
- **Data = baseline + slow drift + other effects of no interest + response$_1$ + … + response$_k$ + noise**
  - How to construct the regressors of interest (responses)?

BOLD Response

- Hemodynamic response (HDR)
  - Brain response to stimulus/task/condition
    - Ideally we want to know the response (activation) at neuronal level, but that is beyond the FMRI capability
  - Indirect measure of neural response: dynamic regulation of blood flow
- Hemodynamic response function (HDF)
  - Mathematical formulation/idealization of HDR
  - BOLD signal is further an indirect measure of brain response
  - HDF bridges between neural response and BOLD signal
- How to build the bridge?
  - One extreme: Assume a fixed-shape (idealized) HDF
  - The other extreme: No assumption about HDR shape
  - Middle ground: major shape + wiggle room for shape adjustment

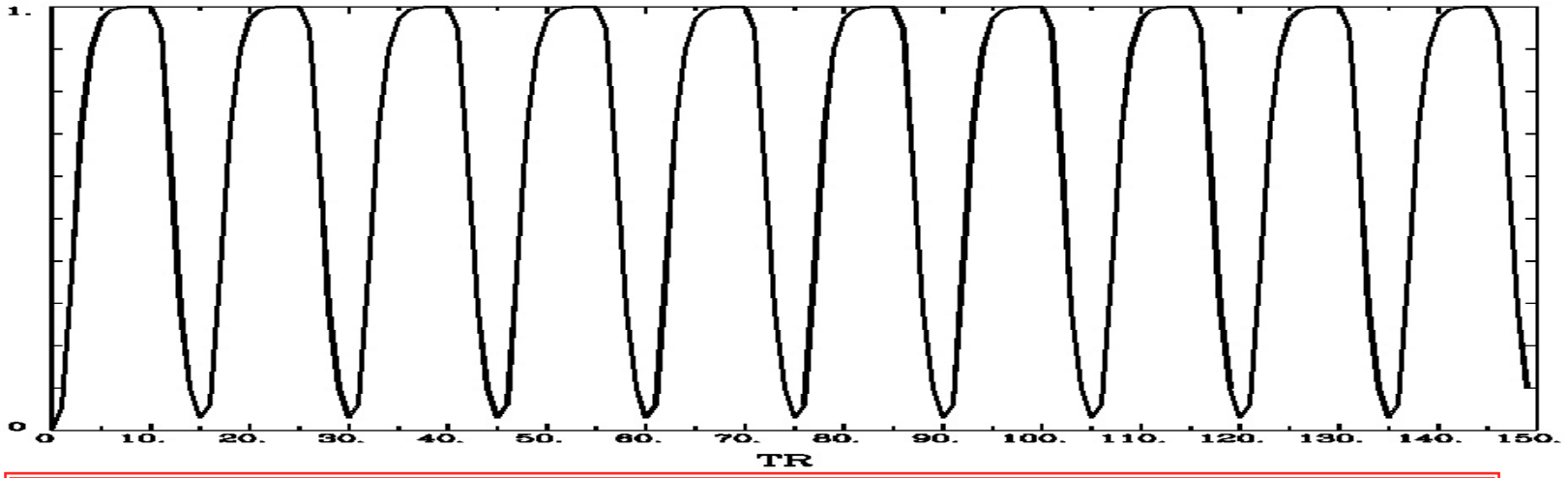
Fixed-Shape IRF

- Assuming a fixed shape $h(t)$ for HDF to an instantaneous stimulus: impulse response function (IRF)
  - GAM(p,q): $h(t) = [t/(p^*q)]^p * exp(p-t/q)$
    - Default IRF: $h(t) = t^{8.6} \exp(-t/0.547)$ [MS Cohen, 1997]
    - A variation: SPMG1 (undershoot)
  - Build HDF based on presumed IRF through convolution
    - Roll IRF $h(t)$ with stimulus timing $S(t)$: $x(t) = h(t) \otimes S(t)$



Fixed-Shape HDF for Block Design

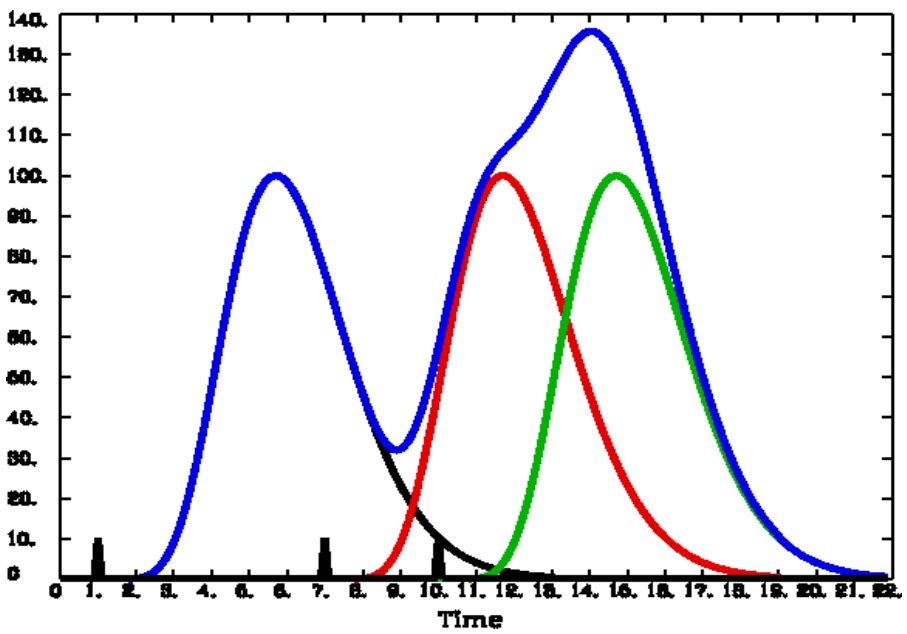
- Assuming a fixed shape $h(t)$ for IRF to an instantaneous stimulus
  - For each block, $h(t)$ is convolved with stimulus timing AND duration (d) to get idealized response (temporal pattern) as an explanatory variable (regressor): BLOCK(d,p)
    - Equivalent to convolving a series of consecutive events
    - Linearity assumed within each block: plateau-like response
    - p: scale HDF to 1 for easy interpretation of β

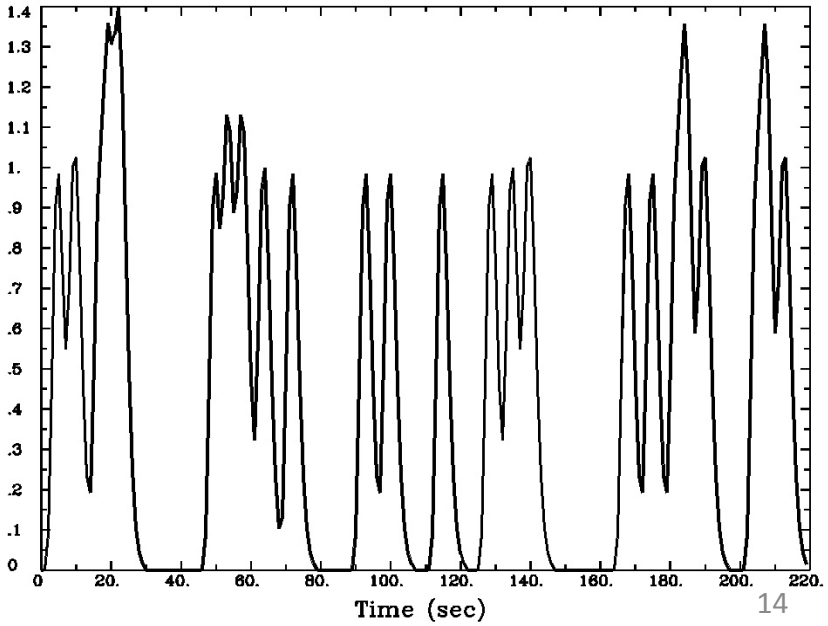


Block: 10 s on and 10 s off; TR=2 s; 150 time points

Fixed-Shape HDF for Event-Related Design

- Fixed shape $h(t)$ for IRF to an instantaneous stimulus
  - For multiple events of a condition/task, $h(t)$ is convolved with stimulus timing to get idealized response (temporal pattern) as an explanatory variable (regressor): GAM(p,q)
    - Linearity assumed when events are close with each other: overlapping impulse responses



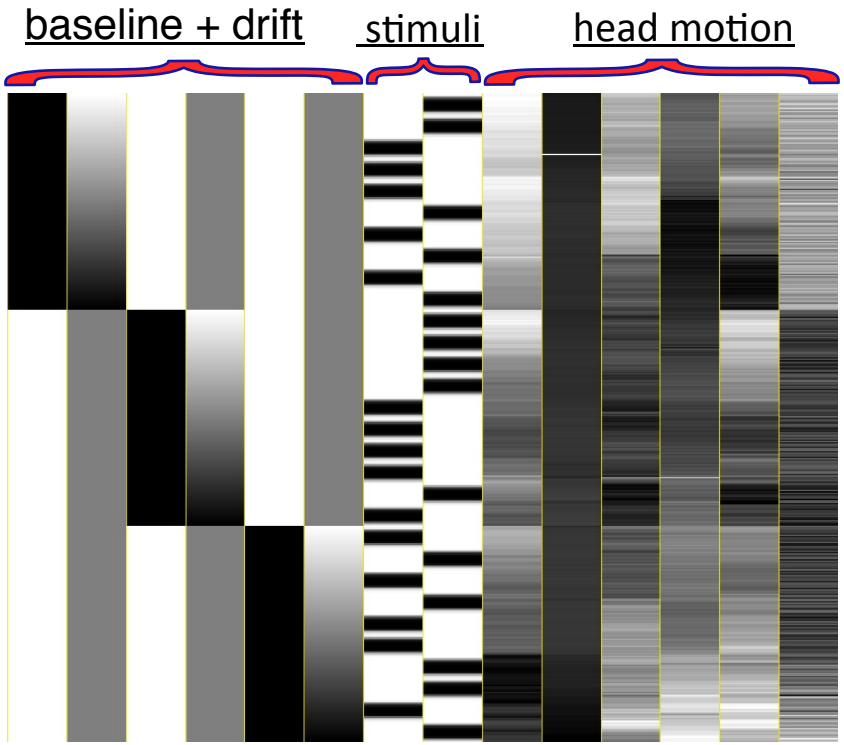


Linear Model with Fixed-Shape IRF

- FMRI data = baseline + drift + other effects of no interest + response_1 + … + response_k + noise
- 'baseline' = baseline + drift + other effects of no interest
  - Drift: psychological/physiological effect, thermal fluctuation
  - Data = 'baseline' + effects of interest + noise
  - Baseline condition (and drift) is treated in AFNI as baseline, an additive effect, not an effect of interest (*cf.* SPM and FSL)!
- $y_i = \alpha_0 + \alpha_1 t_i + \alpha_1 t_i^2 + \beta_1 x_{1i} + \ldots + \beta_k x_{ki} + \ldots + \varepsilon_i$
- $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$, $\mathbf{X} = [1, t, t^2, x_1, x_2, \ldots, x_k, \ldots]$
- In AFNI baseline + slow drift is modeled with polynomials
  - A longer run needs a higher order of polynomials
    - One order per 150 sec
  - With m runs, m separate sets of polynomials needed to account for temporal discontinuities across runs
    - $m(p+1)$ columns for baseline + slow drift: with p-order polynomials
- Other typical effects of no interest: head motion effects

Design Matrix with Fixed-Shape IRF

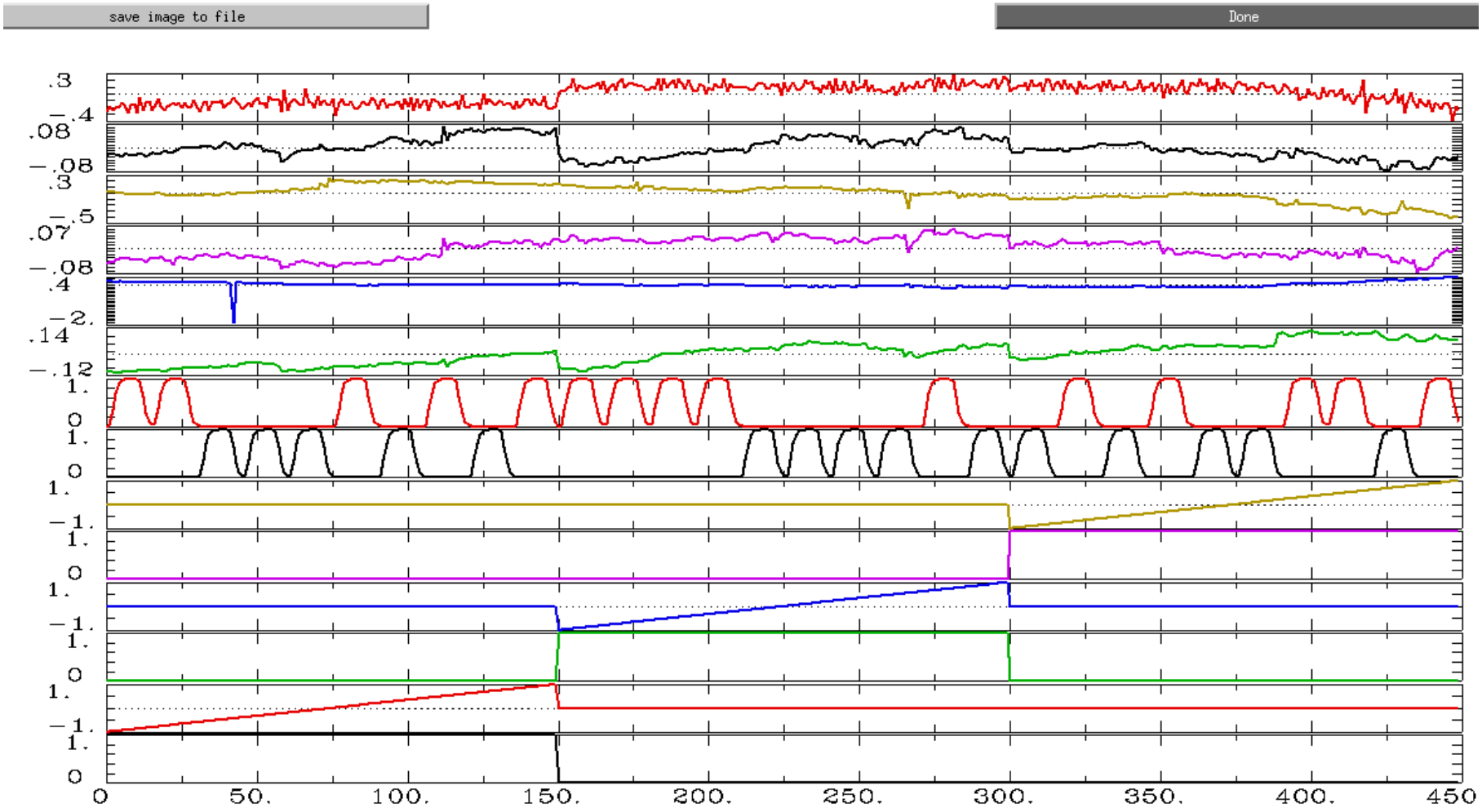
- Voxel-wise (massively univariate) linear model: $y = X\beta + \varepsilon$
  - X: explanatory variables (regressors) – same across voxels
  - y: data (time series) at a voxel – different across voxels
  - β: regression coefficients (effects) – different across voxels
  - ε: anything we can't account for – different across voxels
- Visualizing design matrix $X = [1, t, t^2, x_1, x_2, \ldots, x_k, \ldots]$ in grayscale



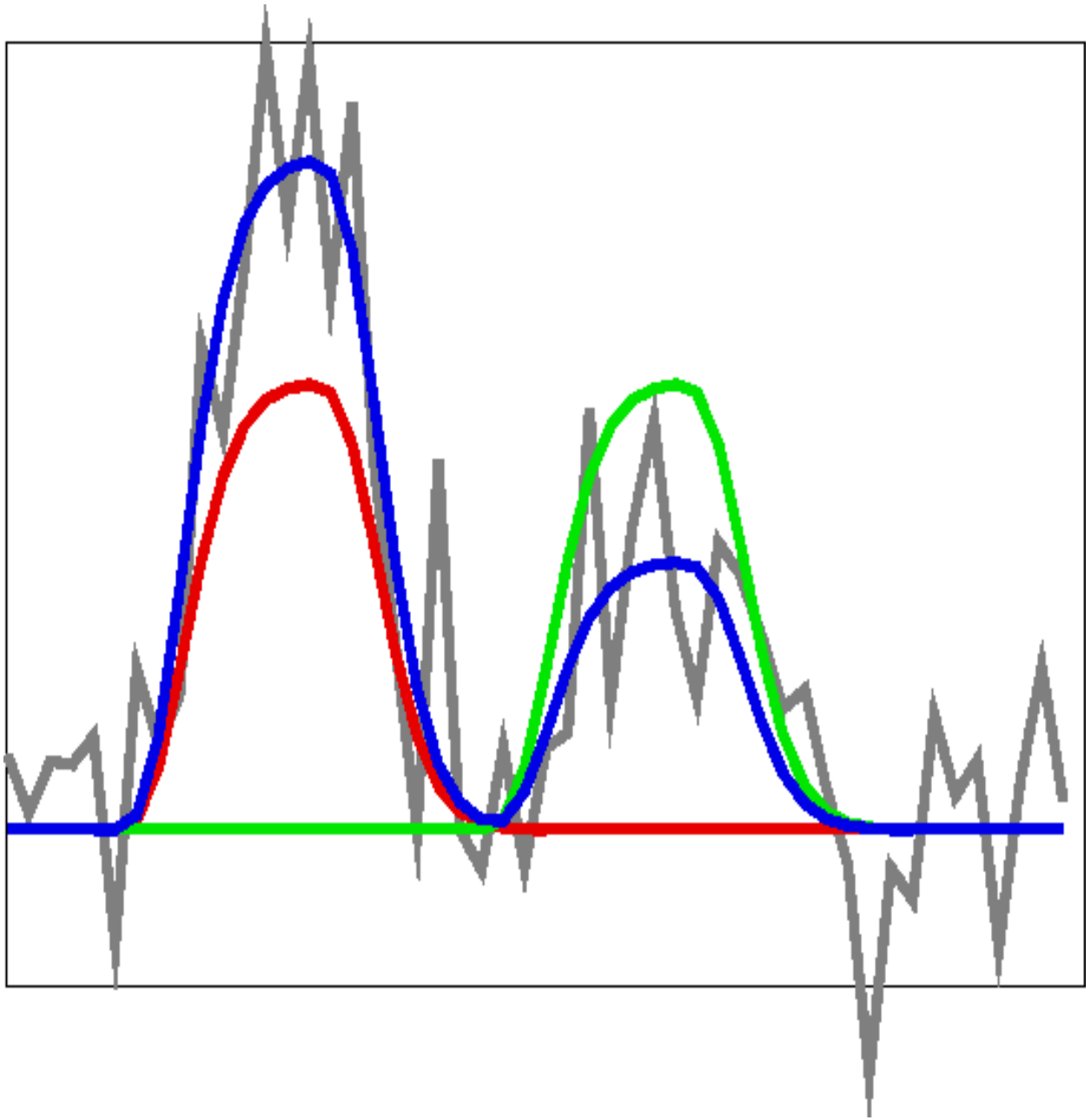
- 6 drift effect regressors
  - linear baseline
  - 3 runs x 2 parameters/run
- 2 regressors of interest
- 6 head motion regressors
  - 3 rotations + 3 shifts

Design Matrix with Fixed-Shape IRF

- Visualizing design matrix X = [1, t, t^2, x_1, x_2, …, x_k, …] in curves



Solving Linear Model



- Gray = data
- **Red** = Expected response shape for #1
- **Green** = Expected response shape for #2
- **Blue** = modeled response = $\beta_1 x_1 + \beta_2 x_2$ where β_1 and β_2 vary from 0.1 to 1.7

- OLS: wiggle around and find β_1 and β_2 that make best fit with blue curve to data

Gray = data = **$1.5x_1 + 0.6x_2$ + noise**

Model Quality Check

- First thing to do!
  - Unfortunately most users in FMRI simply jump to specific effects of interest, their contrasts and their significance. They simply don't pay any attention (or lip service) to overall model performance at all!
- Approaches to judge your model
  - Design matrix report from 3dDeconvolve

```
*+ WARNING: !! in Signal-only matrix:
* Largest singular value=2.37503
* 7 singular values are less than cutoff=2.37503e-07
* Implies strong collinearity in the matrix columns!
```

  - Full *F*-statistic (automatically provided in AFNI)
    - Data = 'baseline' + effects of interest + noise versus
      Data = 'baseline' + noise
  - Determination coefficient R^2 at activated regions (-rout in 3dDeconvolve): poor modeling in FMRI!
    - Block design: ~50%
    - Event-related experiments: 10-20%
  - Modeled vs. not modeled: –fitts and –errts in 3dDeconvolve
    - Fitted curve = 'baseline' + effects of interest
    - Residuals = noise = components we have no idea about

Statistical Testing

- Everything is about contrast!
  - Even true for happiness in life
- Effects (regression coefficients) of interest
  - β: effect relative to baseline condition by default in AFNI
    - $\beta_A = \text{Effect}_A - \beta_{base}$
  - *t*-statistic: significance
- Pairwise comparisons (contrasts)
  - Conditions β_A vs. β_B (*e.g.*, house vs. face)
    - $\beta_A - \beta_B = (\text{Effect}_A - \beta_{base}) - (\text{Effect}_B - \beta_{base}) = \text{Effect}_A - \text{Effect}_B$
  - *t*-statistic: significance
- General linear test – linear combination of multiple effects
  - *t*-statistic: 0.5*happy + 0.5*sad – neutral
- Composite tests
  - *F*-statistic for composite null hypotheses: happy = sad = neutral = 0; or, happy = sad = neutral

Assessing Fixed-Shape IRF Approach

- Used 99% of time: Why popular?
  - Assume brain responds with **same shape** across 4 levels: subjects, activated regions, stimulus conditions/tasks, trials
    - Difference in magnitude β and its significance: what we focus on
    - Strong assumption about four levels of shape information?
  - Easy to handle: one value per effect
  - Works relatively well
    - Block design: shape usually not important due to accumulating effects (modeled via convolution) of consecutive events
      - Really plateau? Same magnitude across blocks?
    - Event-related experiment: OK most of time
      - Linearity when two responses overlap? Same effect across events?
- Not what you want if you
  - care about subtle shape difference across subjects, across regions, across conditions, and across trials
  - improve modeling

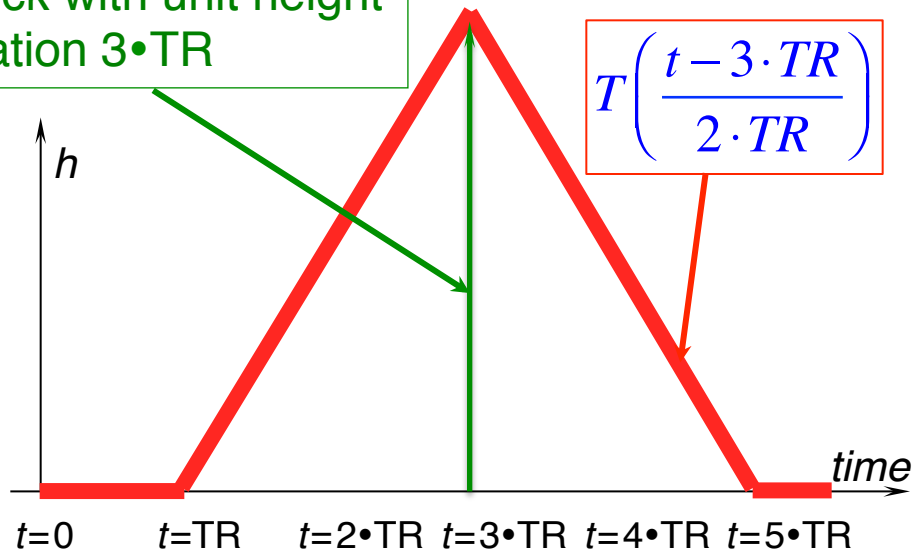
No Constraint on IRF Shape

- Yardstick (or TENT) perspective
  - ➢ Set multiple yardsticks (or tents) at various equally-spaced locations to cover the potential BOLD response period
    - o Each yardstick or TENT is a basis function
  - ➢ BOLD response measured by yardstick heights at all locations
    - o Condition effect is reflected by as many as number of yardsticks
- Yardsticks (percent signal change sticks): TENT functions
  - ➢ Also known as 'piecewise linear splines'

$$T(x) = \begin{cases} 1 - |x| & \text{for } -1 < x < 1 \\ 0 & \text{for } |x| > 1 \end{cases}$$

yardstick with unit height @ location 3•TR

$$T\left(\frac{t - 3 \cdot TR}{2 \cdot TR}\right)$$



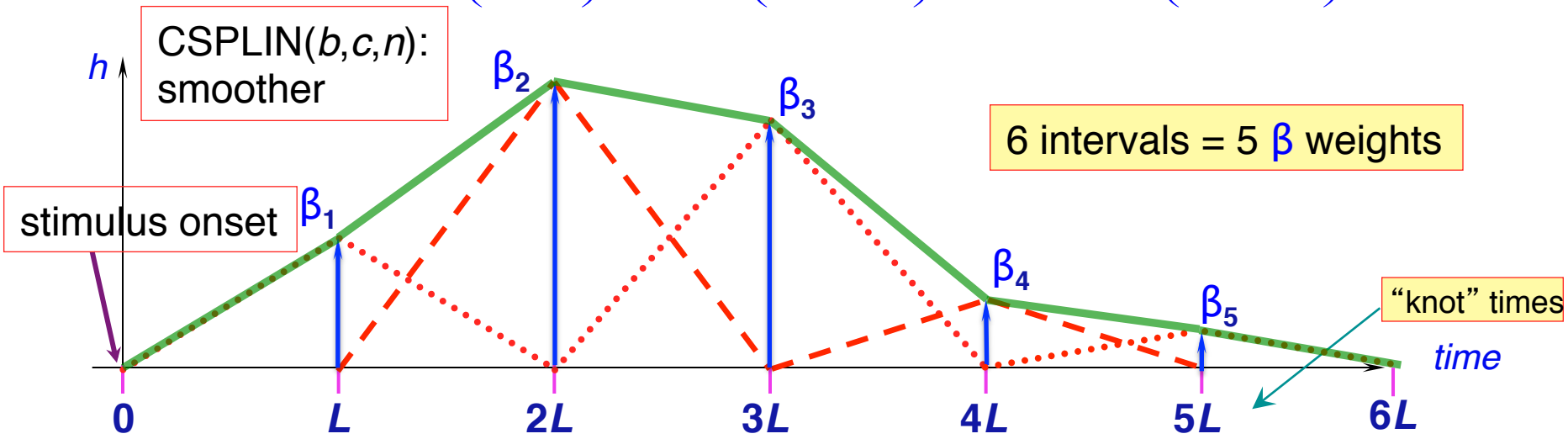
Cubic splines are also available

Tent Functions = Linear Interpolation

A

- 5 equally-spaced tent functions (yardsticks): linear interpolation between "knots" with TENTzero(b,c,n) = TENTzero(0,12,7)

$$h(t) = \beta_1 \cdot T\left(\frac{t-L}{L}\right) + \beta_2 \cdot T\left(\frac{t-2\cdot L}{L}\right) + \cdots + \beta_5 \cdot T\left(\frac{t-5\cdot L}{L}\right)$$



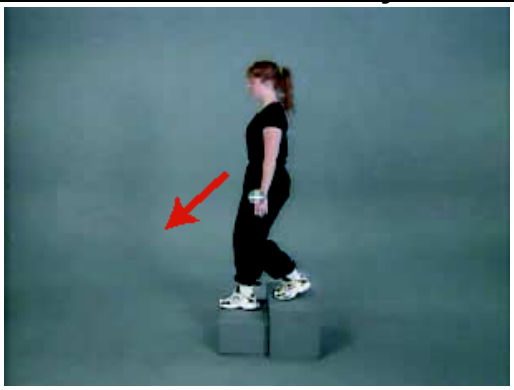
- Tent parameters are easily interpreted as function values (e.g., ***L***: tent radius; β_2 = response (tent height) at time ***t*** = ***2L*** after stimulus onset)
- Relationship of tent spacing ***L*** and TR (***L*** ≥ TR), *e.g.*, with TR=2s, ***L***=2, 4s
- In **uber_subject.py** or **3dDeconvolve** with TENTzero(0, *D*, *n*), specify duration (*D*) of HRF and number (*n*): radius ***L*** = *D*/(*n*-1) with (*n*-2) full tents, each tent overlaps half tent with two neighboring ones.
  - In above example, *D*=12s, then ***L***=2s *n*=7; covering 12s; TENTzero(0,12,7) ~ TENT(2,12,6)

Modeling with TENTs - Example

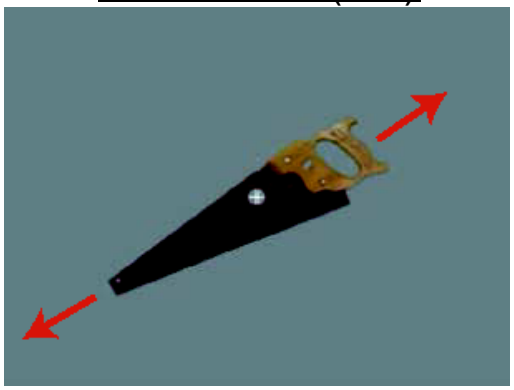
- Event-related study (Beauchamp et al., J Cogn Neurosci 15:991-1001)
  - 10 runs, 136 time points per run, TR=2 s
  - Two factors
    - Object type: human vs. tool
    - Object form: real image vs. points
  - 4 types (2x2 design) of stimuli (short videos)
    - Tools moving (e.g., a hammer pounding) - **ToolMovie**
    - People moving (e.g., jumping jacks) - **HumanMovie**
    - Points outlining tools moving (no objects, just points) - **ToolPoint**
    - Points outlining people moving - **HumanPoint**
  - Goal: find brain area that distinguishes natural motions (**HumanMovie** and **HumanPoint**) from simpler rigid motions (**ToolMovie** and **ToolPoint**)

- **Experiment: 2 x 2 design**

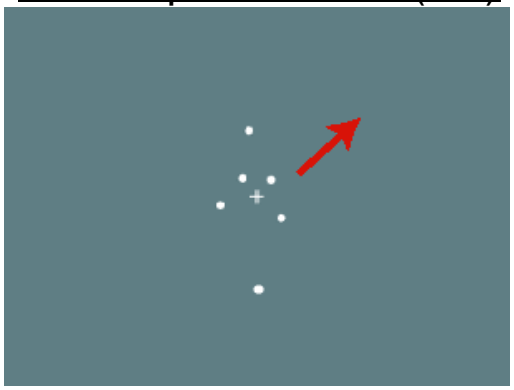
Human whole-body motion (HM)



Tool motion (TM)

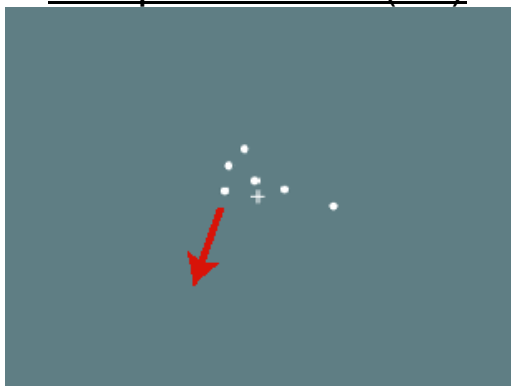


Human point motion (HP)



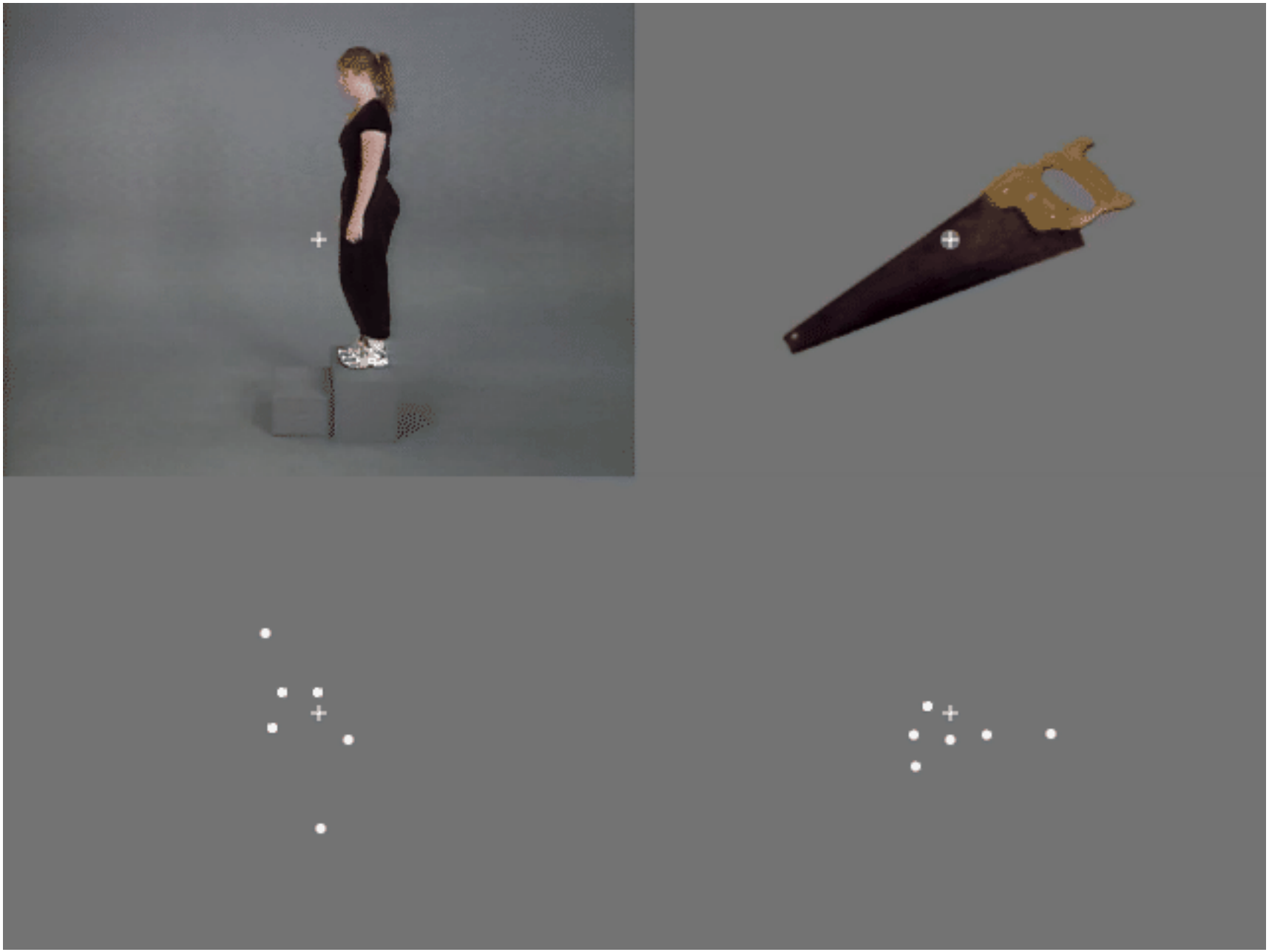
From Figure 1
Beauchamp et al. 03

Tool point motion (TP)



Hypotheses to test:

- Which areas are differentially activated by any of these stimuli (main effect)?
  - point motion versus natural motion? (type of image)
  - human-like versus tool-like motion? (type of motion)
- Interaction effects?
  - Point: human-like versus tool-like? Natural: human-like versus tool-like?
  - Human: point versus natural? Tool: point versus natural?



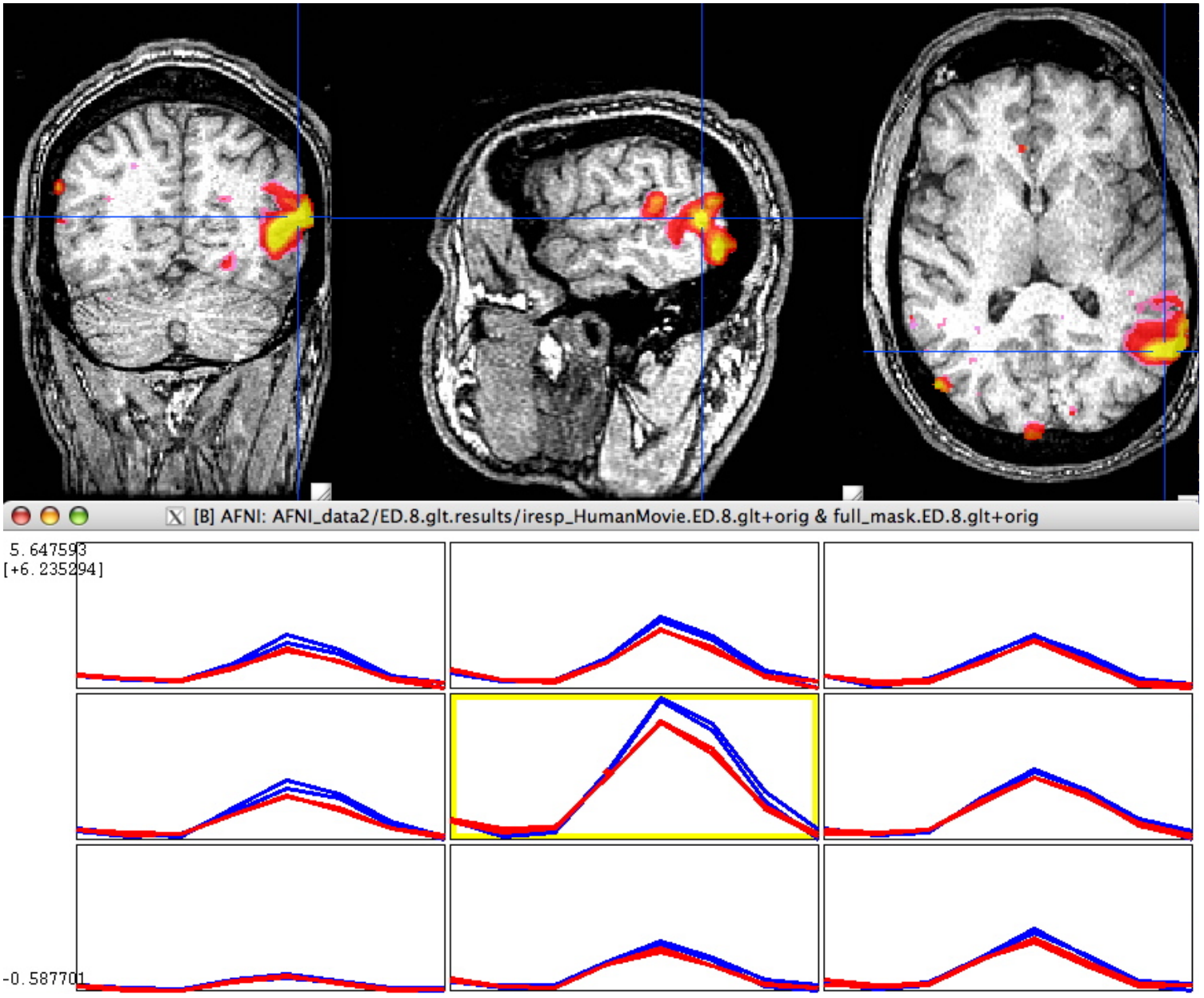
Design Matrix with `TENTzero(0,16,9)`

Baseline + quadratic trend for 10 runs

7 tents per condition × 4 conditions

head motion

Results: Humans vs. Tools



- Color overlay: **Human vs Tool**
- **Blue** (upper) : Human
- **Red** (lower) : Tool

No Constraint on IRF Shape: Deconvolution

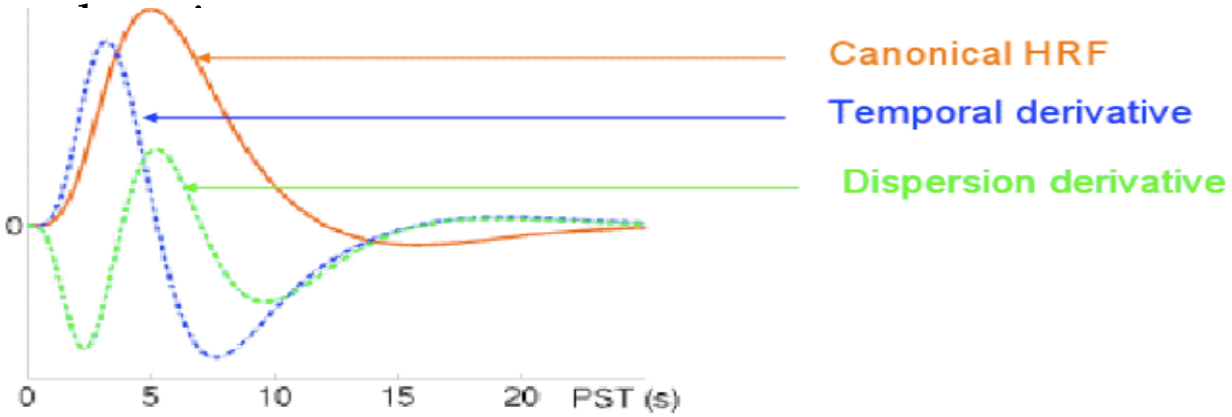
- Deconvolution perspectives: inverse process of convolution
  - IRF ⊗ stimulus = unit BOLD response
    - Like multiplication, we have to know two and estimate the 3rd
  - Fixed-shape approach: Convolution + regression
    - Known: impulse response, stimulus
    - Use convolution to create regressors (hidden: waver or 3dDeconvolve)
    - Response strength (β) estimated via linear model with 3dDeconvolve/3dREMLfit
  - Shape estimation: Deconvolution + regression
    - Known: stimulus + BOLD response; unknown: impulse response
    - HRF ⊗ stimulus = BOLD response (note: HRF, not IRF)
    - HDR estimated as a linear combination of multiple yardsticks (basis TENT functions)
    - Each yardstick (TENT) ⊗ stimulus = regressor
    - Deconvolution: HDF = a set of β's estimated via regression

No Constraint on IRF Shape: Pros + Cons

- What is the approach good at?
  - Usually for event-related experiments, but can be used for BLOCK
    - Multiple basis functions for blocks: within-block attenuation
  - Likely to have more accurate estimate on HDR shape across
    - subject
    - conditions/tasks
    - brain regions
  - Likely to have better model fit
  - Likely to be statistically more powerful on test significance
  - For block design, may detect within-block attenuation
    - Cross-block attenuation?
- Why is the approach not popular?
  - Difficult to summarize at group level
  - A few times more regressors than alternatives: DF's
  - Risk of highly correlated regressors: Multicollinearity
    - May change the number of basis functions
  - Overfitting: picking up something (head motion) unrelated to HDR

Moderate Approach: SPMG1/2/3

- Balance in shape flexibility and basis functions
  - Constrain the HDR shape with a principal basis function
    - SPMG1 (similar to GAM in AFNI): $e^{-t}(a_1 t^{p1} - a_2 * t^{p2})$ where
      $a_1 = 0.0083333333$ $p1 = 5$ (main positive lobe)
      $a_2 = 1.274527\text{e-}13$ $p2 = 15$ (undershoot part)
  - 2 or 3 basis functions: parsimonious, economical
    - SPMG1+SPMG2+SPMG3
    - SPMG2: temporal derivative capturing differences in peak latency
    - SPMG3: dispersion derivative capturing differences in peak



Multicollinearity

- Voxel-wise regression model: $y = X\beta + \varepsilon$
  - Regressors in design matrix $X = [1, t, t^2, x_1, x_2, \ldots, x_k, \ldots]$
- Multicollinearity problem
  - Two or more regressors highly correlated
  - Difficult or impossible to tear apart the effects
- Multicollearity scenarios
  - Collinearity - $x_i = \lambda x_j$: model specification error, *e.g.*, 2 identical regressors (mistake in stimulus timing specifications)
  - Exact multicollinearity: linear among regressors: faulty design (rare)
  - High degree of correlation (+ or -) among regressors: design problem
    - *E.g.*, cue + movie watching
  - Too many basis functions
- Diagnosis tools: ExamineXmat.R, timing_tool.py, xmat_tool.py

Serial Correlation in Residuals

- Why temporal correlation?
  - In the residuals (not the time series data)
  - Short-term psychological and physiological effect
  - Other unknown reasons
- What is the impact of temporal correlation?
  - With white noise assumption, β's are unbiased, but the statistics tend to be inflated
  - Little impact on group analysis if only taking β's
  - May affect group analysis if considering effect reliability
- Approach in AFNI
  - ARMA(1,1) for residual time series
  - Slightly different from other packages

Dealing with Multiple Runs

- Concatenation?
  - ➢ Analyze each run separately: AFNI, FSL
    - Have to have enough repetitions per run
    - Can test cross-run difference (trend, habituation) at group level
    - Summarize multiple β's before group analysis
  - ➢ Concatenate but analyze with separate regressors across runs for each condition type: AFNI, SPM
    - Can test cross-run difference (trend, habituation, etc.) at both individual and group level
    - Summarize multiple β's before group analysis
  - ➢ Concatenate but analyze with same regressor across runs for each condition type: default in AFNI
    - Assume no attenuation across runs
- Cross-block (or cross-event) attenuation
  - Crude method: -stim_times_IM

Percent Signal Change

- Why conversion? Comparable across subjects
  - BOLD data don't have any physical/physiological meaning
  - Baseline is different across subjects
  - It's the relative changes that can be compared across subjects
- AFNI approach
  - Pre-processing: data scaled by voxel-wise mean
    - % signal change relative to mean, not exactly to baseline
    - Difference is tiny: less than 5%
  - Tied with modeling baseline as additive effects in AFNI
    - Sometimes baseline explicitly modeled in SPM and FSL
    - Global mean scaling (multiplicative) for whole brain drift
    - Grand mean scaling for cross-subject comparison: not %
    - Global and grand mean scaling, although not usually practiced, can be performed in AFNI if desirable

Percent Signal Change

- Why not scaled β's by real baseline???
  - ➢ No catenation: scale β per run by the run's baseline
    - Sample size in each run could be low
    - Have to summarize multiple β's before group analysis
    - Better convert to percent signal change at run level before summing over runs
    - Be careful when motion parameters included in model
      - Uber_subject.py automatically demeans the head motion regressors
  - ➢ Catenation: problematic
    - Baseline may be different across runs
    - Effects are not comparable across runs

Lackluster Performance in Modeling

- Essentially, all models are wrong, but some are useful (G.E.P. Box)
- Noisy data: easy excuse!
- Regressors: idealized response or yardstick
  - We get what we're looking for
  - It may miss something when we fail to recognize it
- Lots of variability across trials
  - Amplitude modulation if behavioral data are available
  - Model each trial separately
- Linearity assumptions
  - Data = baseline + drift + respone1 + resonse2 + … + noise
  - When a trial is repeated, response is assumed same
  - Response for a block = linearity (no attenuation)
- Poor understanding of BOLD mechanism

Summary

- Basics of linear model
- FMRI experiment types
  - Block design; Event related experiment; Mixed
- FMRI data decomposition: three components
  - Baseline + slow drift; Effects of interest; Unknown
  - Effects of interest - understanding BOLD vs. stimulus: IRF
- Modeling with fixed-shape IRF: GAM(p,q), BLOCK(d,p)
- Modeling with no assumption about IRF shape
  - TENT(b,c,n), CSPLIN(b,c,n)
- Modeling with one major IRF plus shape adjustment
  - SPMG1/2/3
- Other issues
  - Multicollinearity
  - Catenation
  - Percent signal change