FMRI Task-Based Data Analysis at the Individual Level

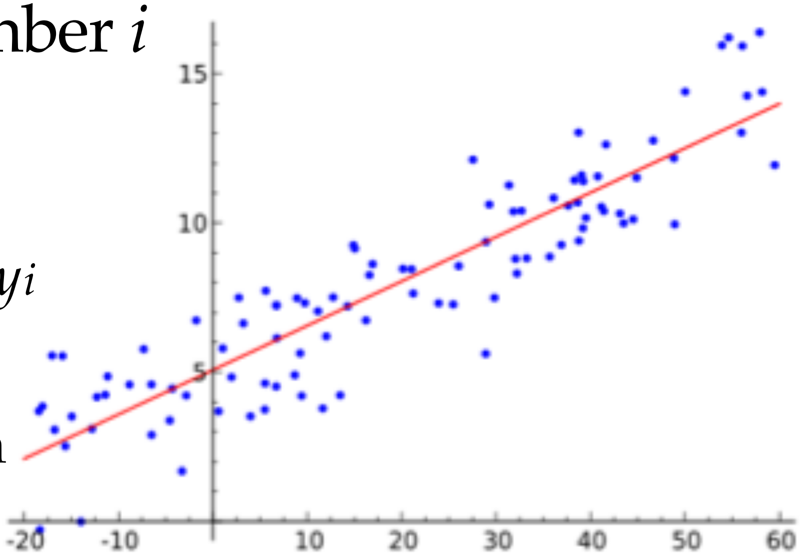
SSCC/NIMH/NIH/DHHS/USA/Earth

Overview

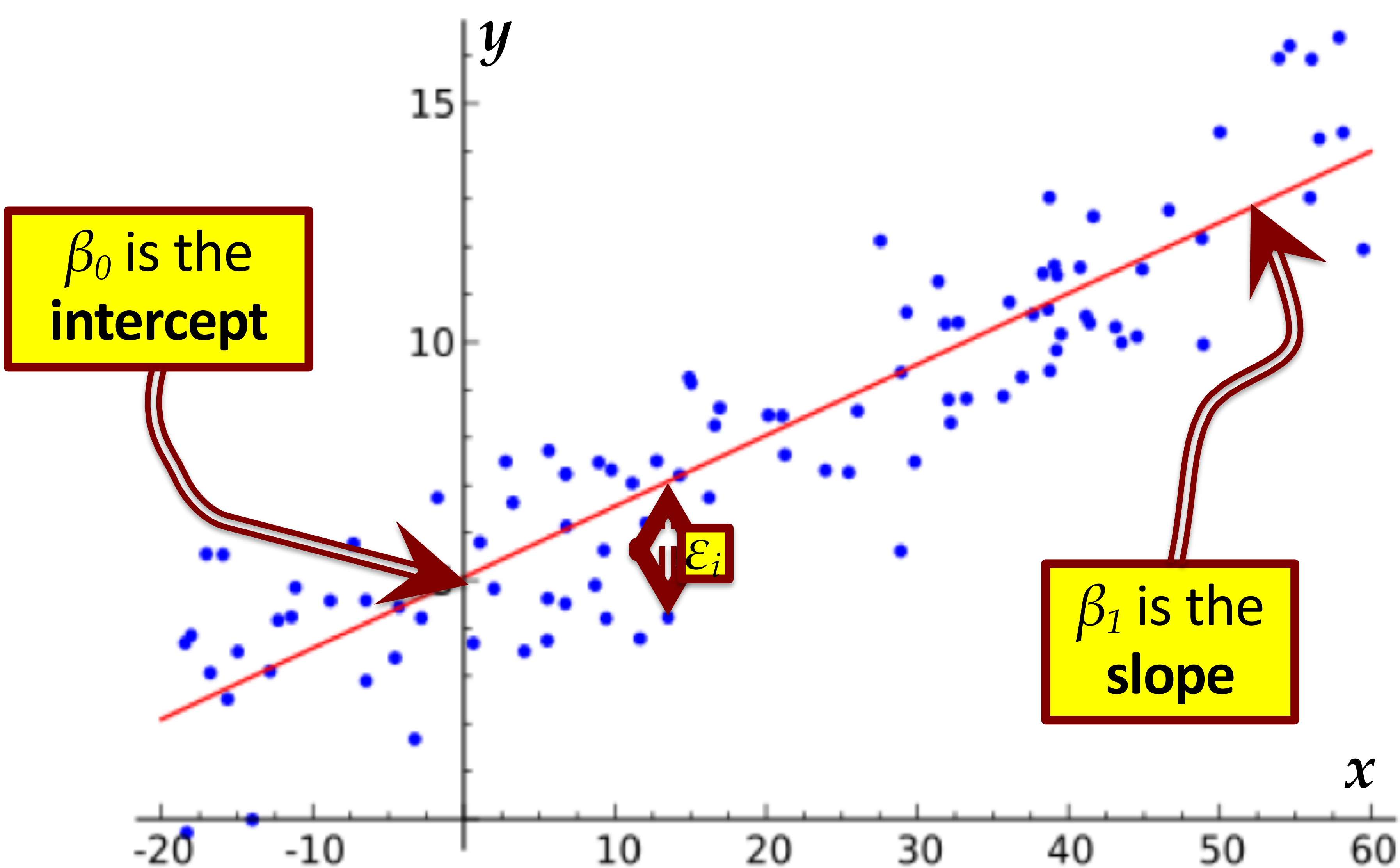
- Basics of linear models for data analysis
- FMRI data decomposition: three components
  - **Baseline + slow drift + effects of no interest**; **Effects of interest**; **Noise**
  - Effects of interest – understanding BOLD vs. stimulus
    - IRF and HRF and HDR
- Three modeling strategies
  - Fixed-shape HRF
  - Variable HRF shape
  - Fixed major HRF shape plus a little shape adjustment
- Other issues
  - Multicollinearity
  - Run catenation
  - Percent signal change

Basics of Linear Modeling

- **Regression**: finding a relationship between a response/outcome (dependent) variable and one or more explanatory (independent) variables (**regressors**)
  - Also called **linear model** or **linear regression**
- Equations
  - i=index of data = 0, 1, 2 … N-1 (total of N data points)
  - x_i=explanatory model (known value) for data point number i
  - y_i=data value for data point number i
  - $y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$ **or** $y_i \approx \beta_0 + \beta_1 x_i$
  - β_0 and β_1 are **model fit parameters**
    - to be calculated from the x_i and y_i
  - ε_i are the **residuals**
    - what are left after the regression
    - assumed to be **random noise**



$$y_i = \beta_0 + \beta_1 x_i + \varepsilon_i \quad \textbf{or} \quad y_i \approx \beta_0 + \beta_1 x_i$$



Modeling with Vectors and Matrices

- Write the model $y_i \approx \beta_0 + \beta_1 x_i$ out in columns (**vectors**)

$$\underbrace{\begin{bmatrix} y_0 \\ y_1 \\ y_2 \\ \cdots \end{bmatrix}}_{\text{data vector}} \approx \begin{bmatrix} 1 \\ 1 \\ 1 \\ \cdots \end{bmatrix} \beta_0 + \begin{bmatrix} x_0 \\ x_1 \\ x_2 \\ \cdots \end{bmatrix} \beta_1 = \underbrace{\begin{bmatrix} 1 & x_0 \\ 1 & x_1 \\ 1 & x_2 \\ \cdots & \cdots \end{bmatrix}}_{\text{N×2 matrix}} \begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix}$$

- In **vector-matrix** form (**bold** letters for vectors and matrices)
  - $\mathbf{y} \approx \mathbf{X}\,\boldsymbol{\beta}$ or with residual vector $\mathbf{y} = \mathbf{X}\,\boldsymbol{\beta} + \boldsymbol{\varepsilon}$
- By writing it out this way, the equations become more compact and easier to look at and easier to understand
- Each column of **X** matrix is a **regressor** or **model component**
- We assume the columns of **X** are known ("the model"), and that data vector **y** is known (measured)
- Goal is to compute **parameter vector** **β** (and statistics about **β**)
- Most of this talk: where do we get **X** for FMRI task analysis?

Solving a Linear Model

Vector **y** is sum of matrix **X** times vector β plus residuals ε

- Solution for linear regression $\mathbf{y} = \mathbf{X}\beta + \varepsilon$
  - "Project" data **y** onto the space of explanatory variables (**X**)
  - **OLS** formula for solution: $\hat{\boldsymbol{\beta}} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{y}$
  - Columns of **X** are the **model** for data vector **y**
- Meaning of coefficient: β_k value is slope, marginal effect, or effect size associated with **regressor** number k [column k in **X**]
- β_k value says how much of regressor number k is needed to fit the data "best" – in the **O**rdinary **L**east **S**quares sense
  - That is, the sum of the squares of ε_i is made as small as possible
- If we don't care about regressor number k, then we don't care about the value of β_k
  - But we included regressor number k in the model because it was needed to fit some part of the data
  - **Regressors of no interest** make up the global Null Hypothesis in the model – in AFNI, we call these regressors the **baseline model**

Statistics in a Linear Model

- Various statistical tests carried out after solving for **β** vector
- Some examples, with particular null hypotheses H_0
  - Student *t*-test for each β_i of interest

$$H_0\text{:}\ \beta_3 = 0$$

  - Student *t*-test for linear combination of some β_i values = general linear test (GLT)

$$H_0\text{:}\ \beta_3 - \beta_5 = 0$$

$$H_0\text{:}\ 0.5^*(\beta_3 + \beta_4) - \beta_5 = 0$$

  - *F*-test for composite null hypothesis

$$H_0\text{:}\ \beta_3 = \beta_4 = \beta_5$$

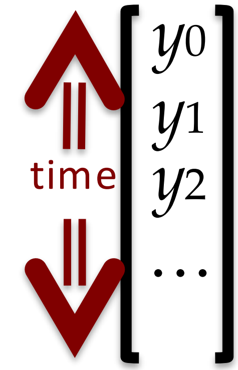
$$H_0\text{:}\ \beta_3 = \beta_4 = \beta_5 = 0$$

  - Omnibus or Full *F*-test for the entire model

H_0: all β_i values of interest are 0

Linear Model with FMRI

- Time series regression: data vector **y** is time series = all values from ***one*** voxel throughout multiple image acquisitions (TRs)



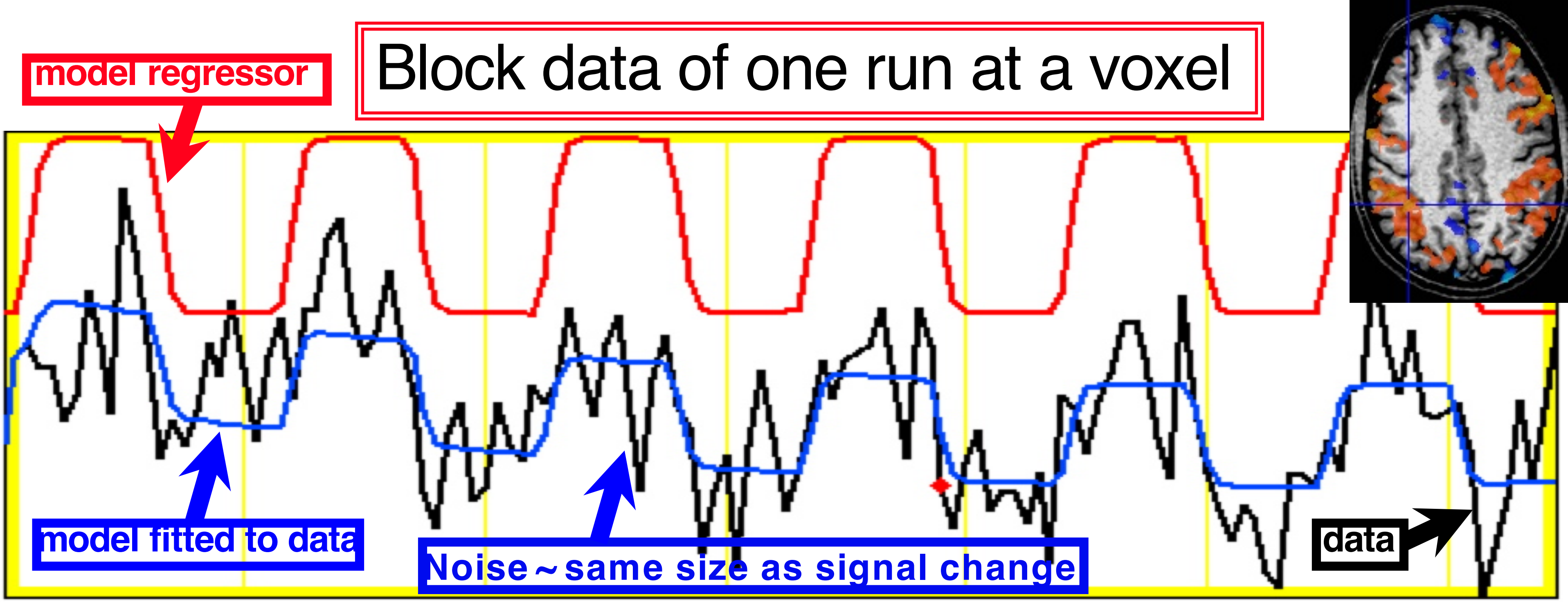
- Regressors: idealized BOLD response curves
  - We can only find what we're looking for
  - Regression will miss something if we do not look for it
    - So we must include regressors of no interest, so we can model things like baseline drifting up or down
  - Regressor construction requires decisions
  - Don't want to **over**-fit or **under**-fit data
- Same model matrix **X** for all voxels in the brain
  - Simultaneously solve all the models (1 for each voxel)
  - Voxel-wise analysis = "massively univariate" method

FMRI Data

- Data partition: **Data = Signal + Noise**
  - **Data** = acquisition from scanner (voxel-wise time series)
  - **Signal** = BOLD response to stimulus; effects of interest + no interest
    - **We don't actually know the real signal shape to look for*!!!***
    - Look for idealized task responses by assuming a **fixed shape** for BOLD effect (FMRI response) for each task trial
    - ***Or*** search for signal shape via repeated trials and **basis functions**
    - Of interest: effect size (response amplitude) for each task: **beta**
    - Of no interest: baseline, slow drifts, head motion effects, …
  - **Noise** = components in data that interfere with signal
    - Practically: the part of the data we can't explain with the model
    - Will have to make some assumptions about its probability distribution – to be able to carry out the statistical tests
- **Data = baseline + slow drift + other effects of no interest + response$_1$ + … + response$_k$ + noise**
- How to construct the regressors of interest (responses)?

Block data of one run at a voxel

model regressor



Block: 27 s “on” / 27 s “off”; TR=2.5 s; 130 time points

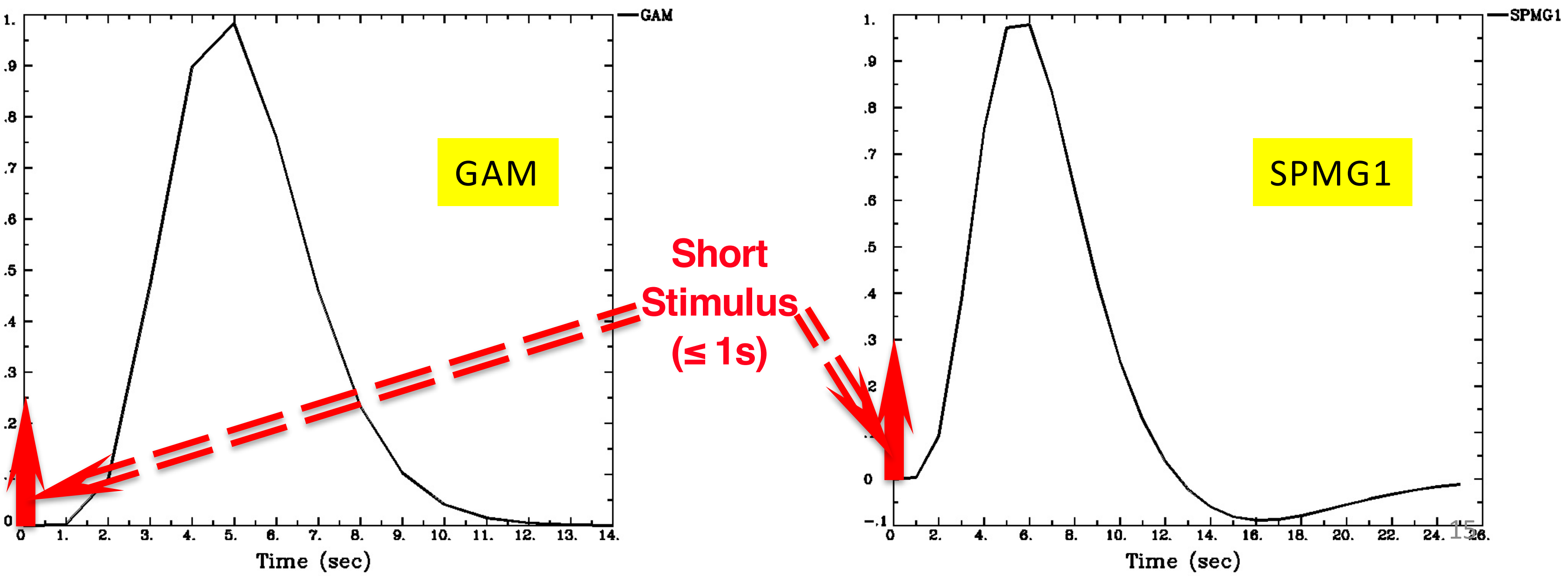
- This is “best” voxel; most voxels are not fitted as well as this
- Data drifts downwards – this effect is captured in the model fit by baseline drift regressors
  - If we did *not* model for drift, our fit would not be as good
- Activation amplitude and shape vary across blocks
  - Reasons why? We can only guess
  - Habituation? Attention? Noise?

BOLD Response

- Hemodynamic response (**HDR**)
  - Brain+FMRI response to stimulus/task/condition
  - Indirect measure of neural response: brain activation➔ changes in blood oxygen➔changes in FMRI signal
- Hemodynamic response function (**HRF**)
  - Mathematical formulation/idealization of HDR for ***one*** full stimulus interval
  - HRF bridges between neural response (what we like) and BOLD signal (what we measure)
- How to build the bridge?
  - Most simple: Assume a fixed-shape (idealized) HRF
  - Most complex: No assumption about HDR shape
    - Basis function expansion of HRF shape and size
  - In the middle: 1 major fixed shape + a little space for shape adjustment

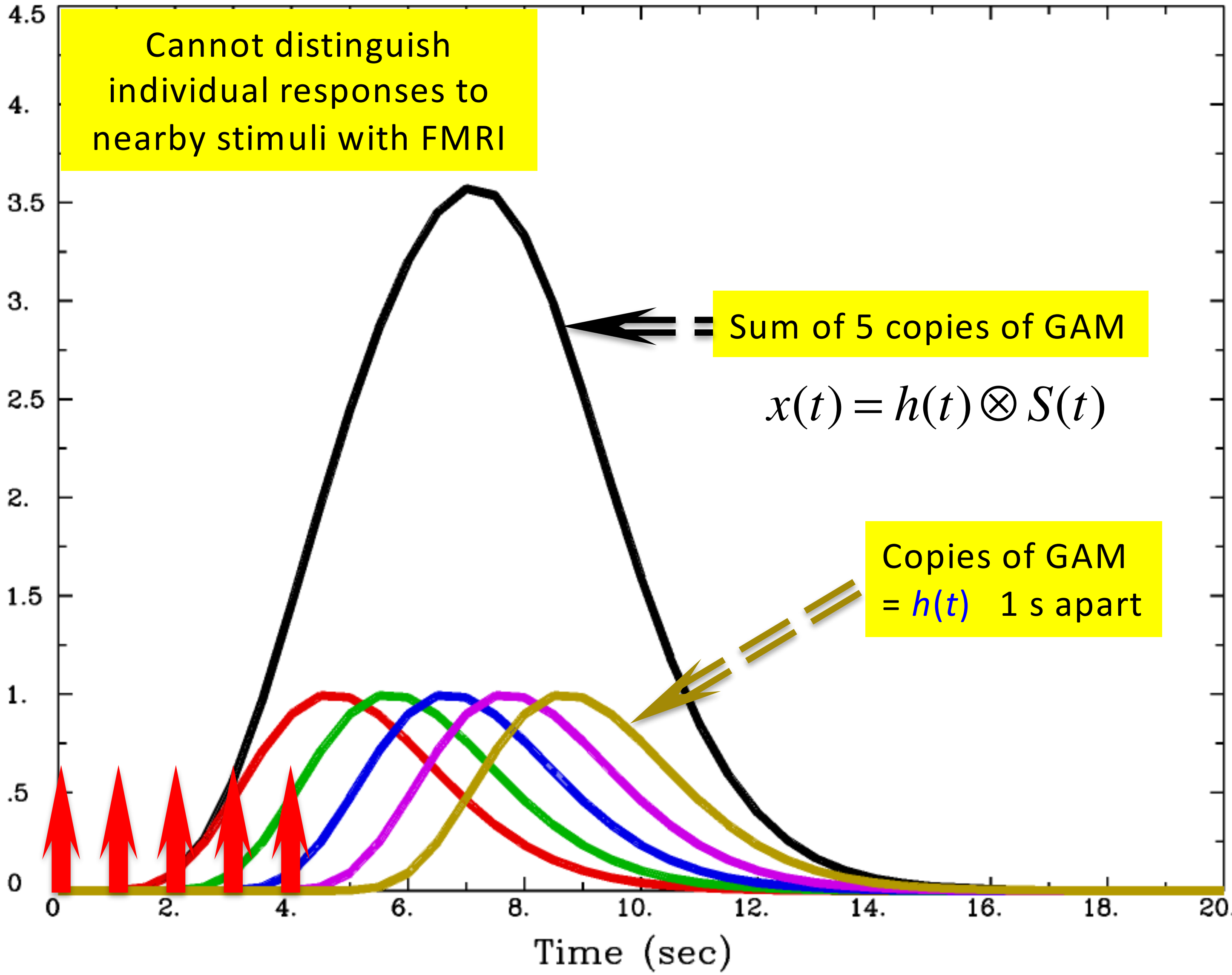
Fixed-Shape HRF – 1 s Stimulus

- Assume a fixed shape $h(t)$ for HRF to an **instantaneous** (very short) stimulus: impulse response function (**IRF**)
  - GAM(p,q): $h(t) = t^p \exp(t/q)$ for power p and time q
    - Sample IRF: $h(t) = t^{8.6} \exp(-t/0.547)$ [MS Cohen, 1997]
    - A variation: SPMG1 (undershoot is added in)
  - Build HRF based on presumed IRF through **convolution**
    - Combine IRF $h(t)$ with stimulus timing $S(t)$: $x(t) = h(t) \otimes S(t)$



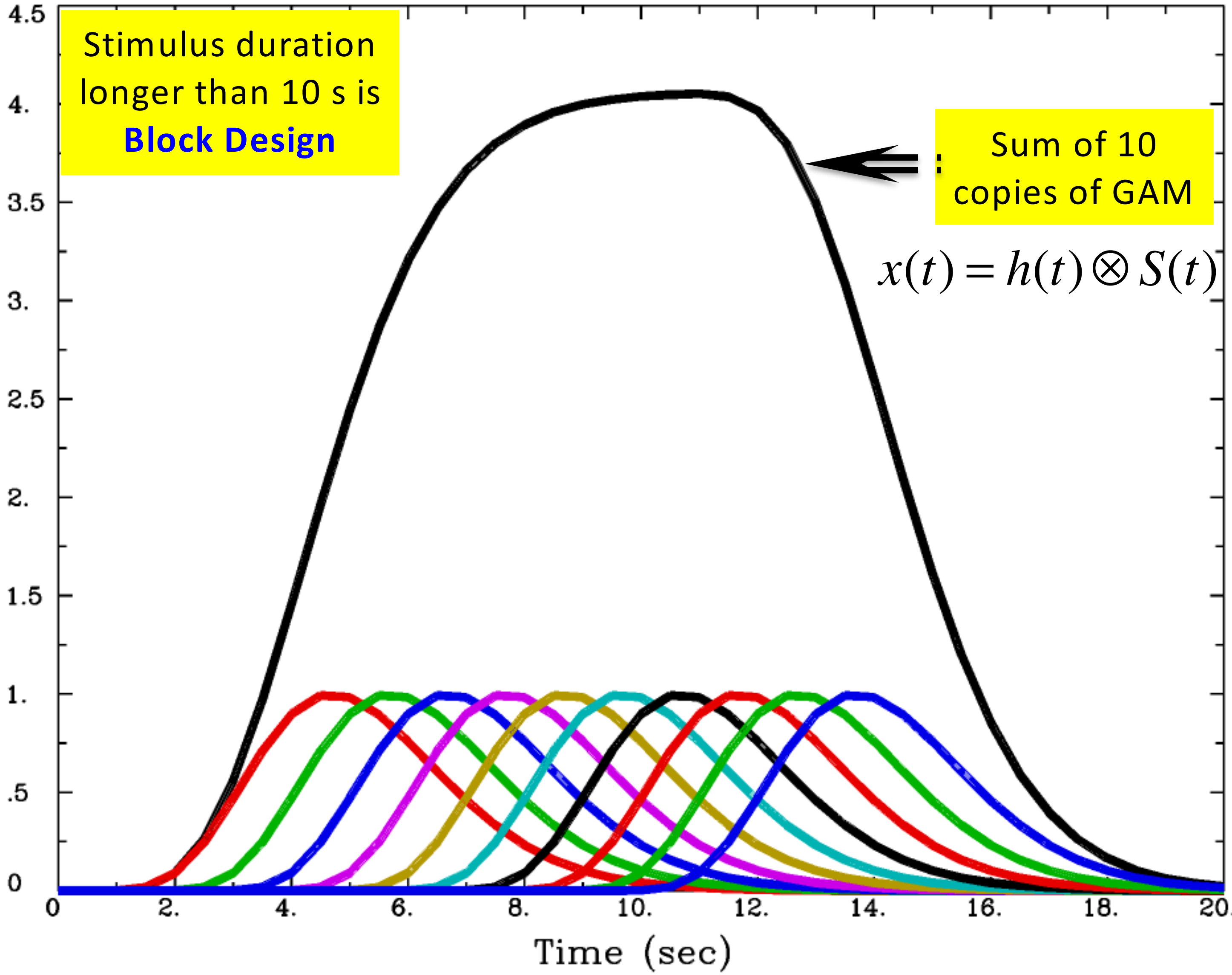
Fixed-Shape HRF – 5 s Stimulus

- Combine IRF $h(t)$ with stimulus timing $S(t)$:



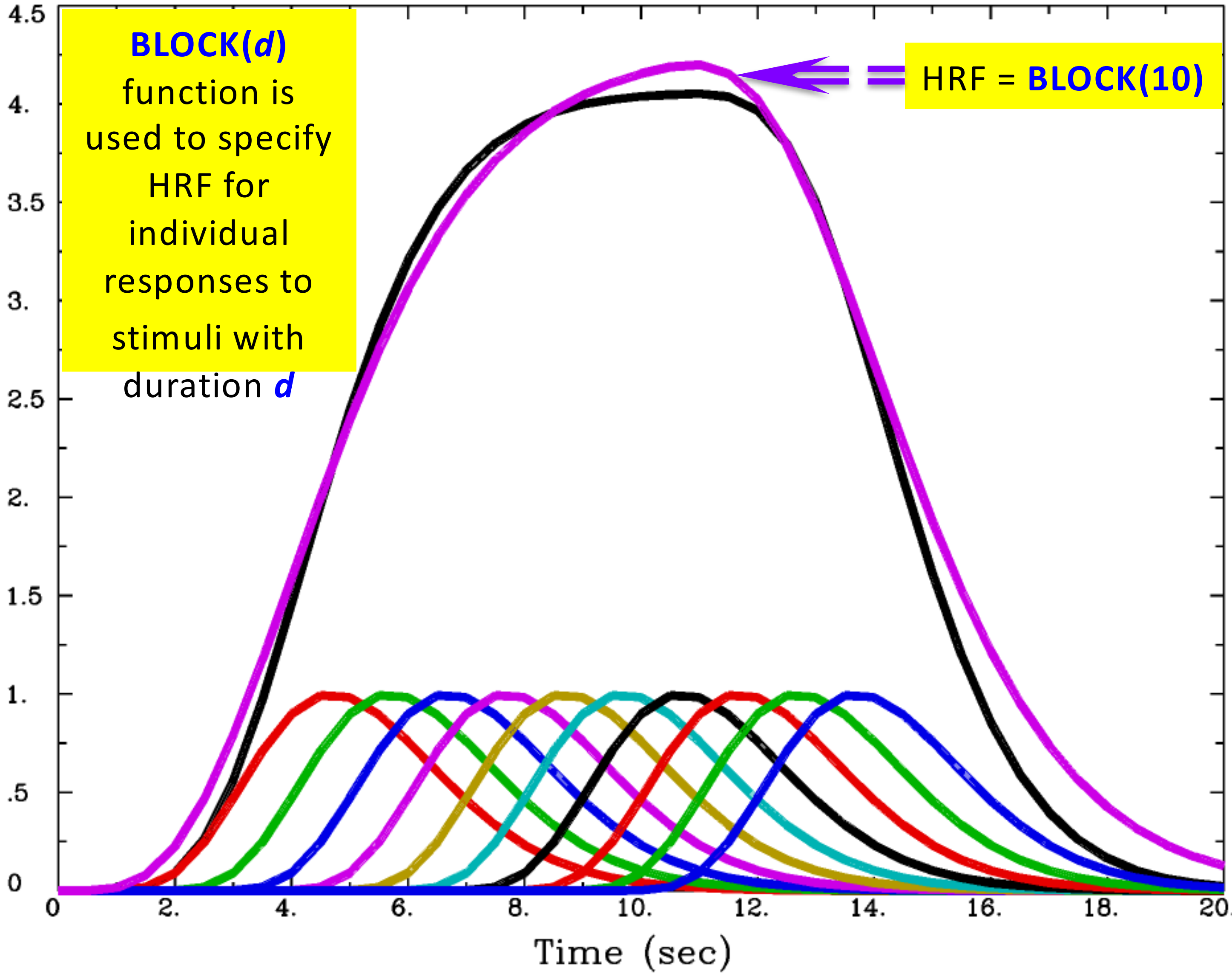
Fixed-Shape HRF – 10 s Stimulus

- Combine IRF $h(t)$ with stimulus timing $S(t)$:



Fixed-Shape HRF – 10 s Stimulus

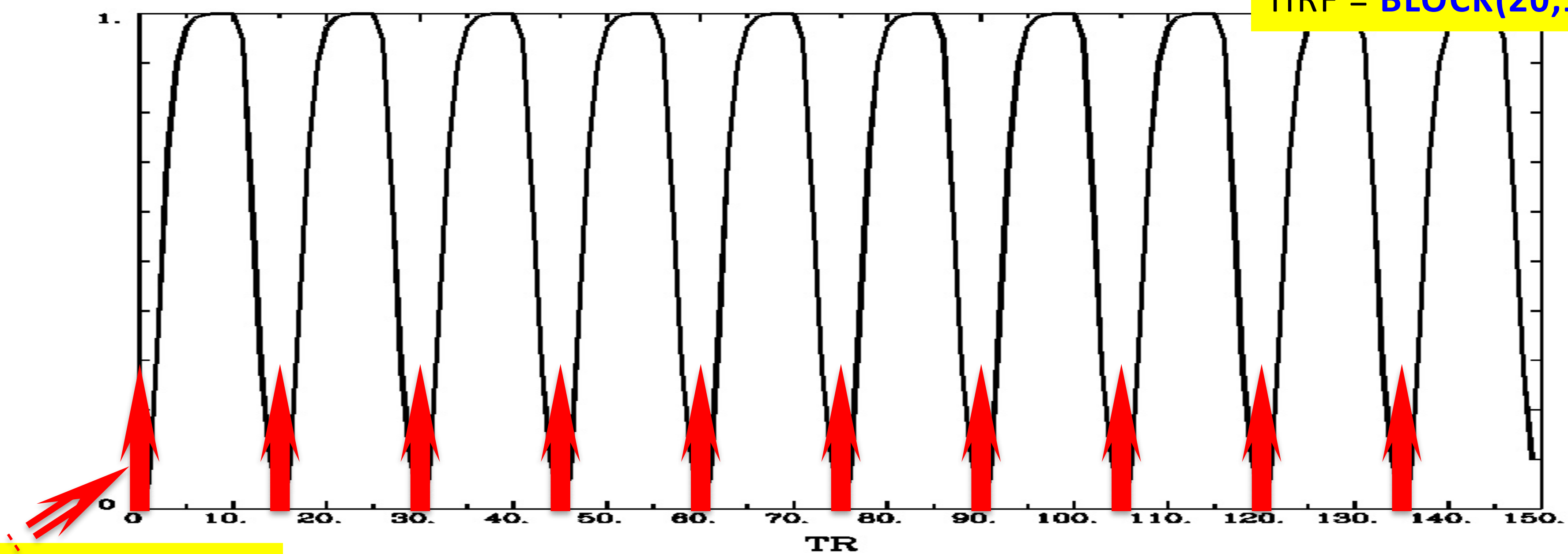
- With the '**BLOCK(10)**' function in AFNI



Fixed-Shape HRF for Block Design

- Assuming a fixed shape *h*(*t*) for IRF to an **instantaneous** (very short) 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): HRF = **BLOCK(*d*,*p*)**
    - **Equivalent to adding up a series of consecutive events**
    - scale HRF to *p*=1 for easy interpretation of β

HRF = **BLOCK(20,1)**

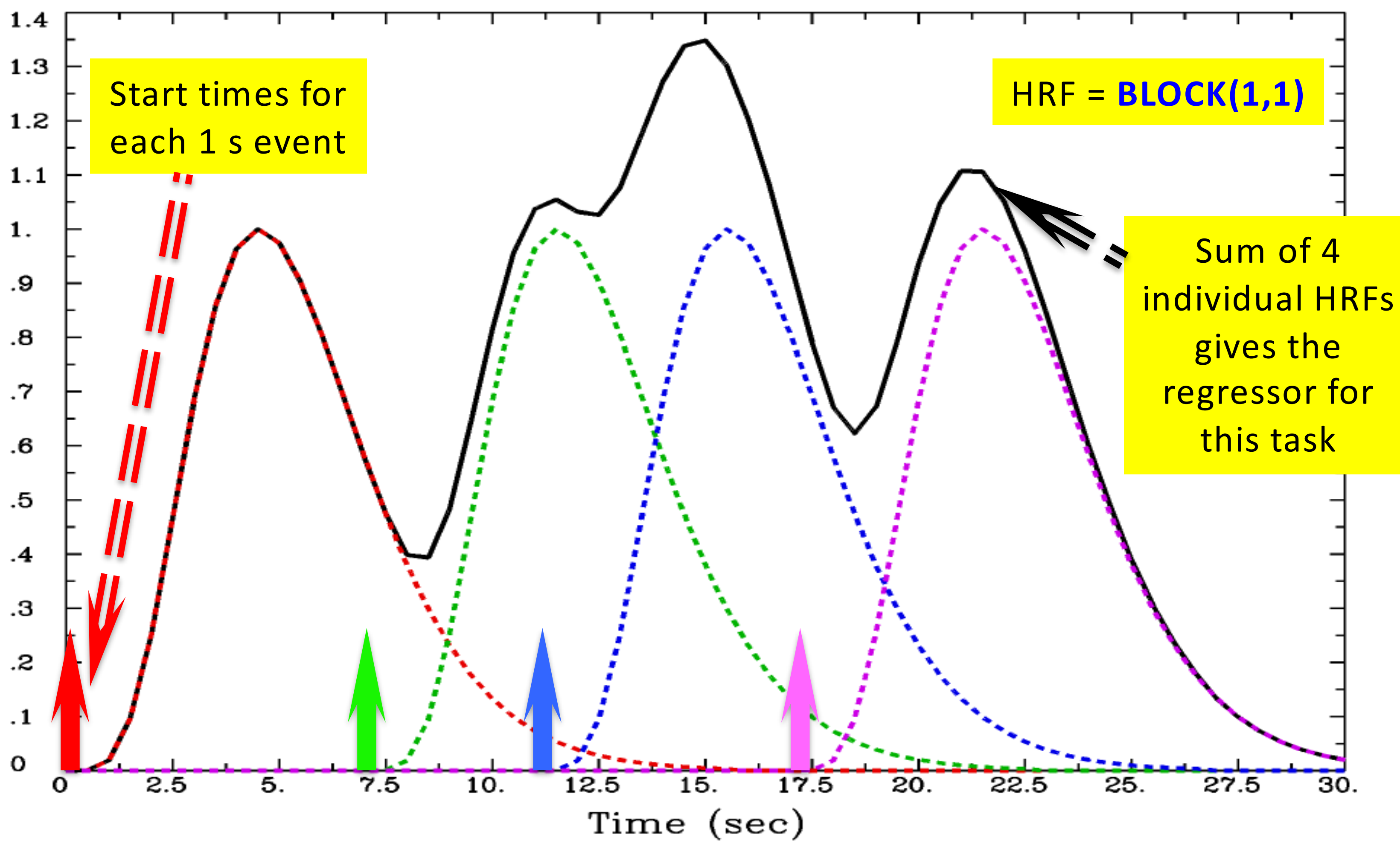


Start times for each block

Block: 20 s on and 10 s off; TR=2 s; 150 time points

Fixed-Shape HRF for Event-Related Design

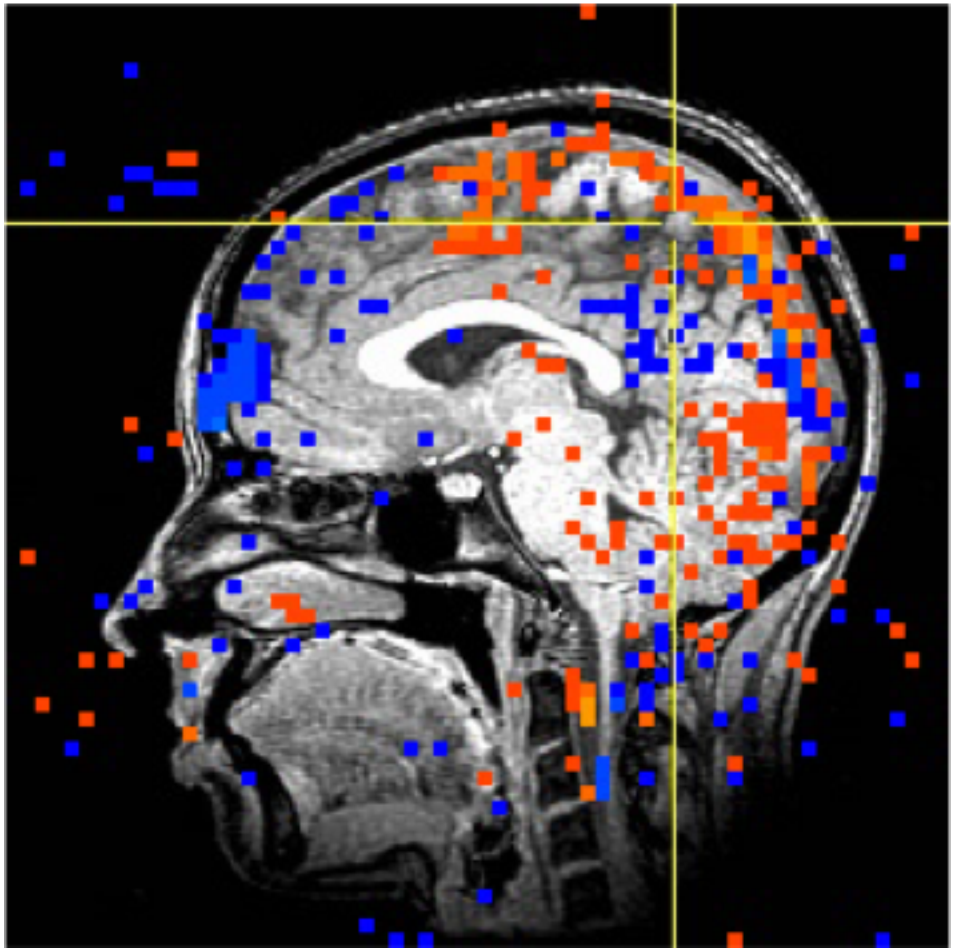
- The **BLOCK** HRF shape is useful with event-related experiment designs
- Just use a short duration, such as 1 second
- Real experiments have more than 4 task repetitions!



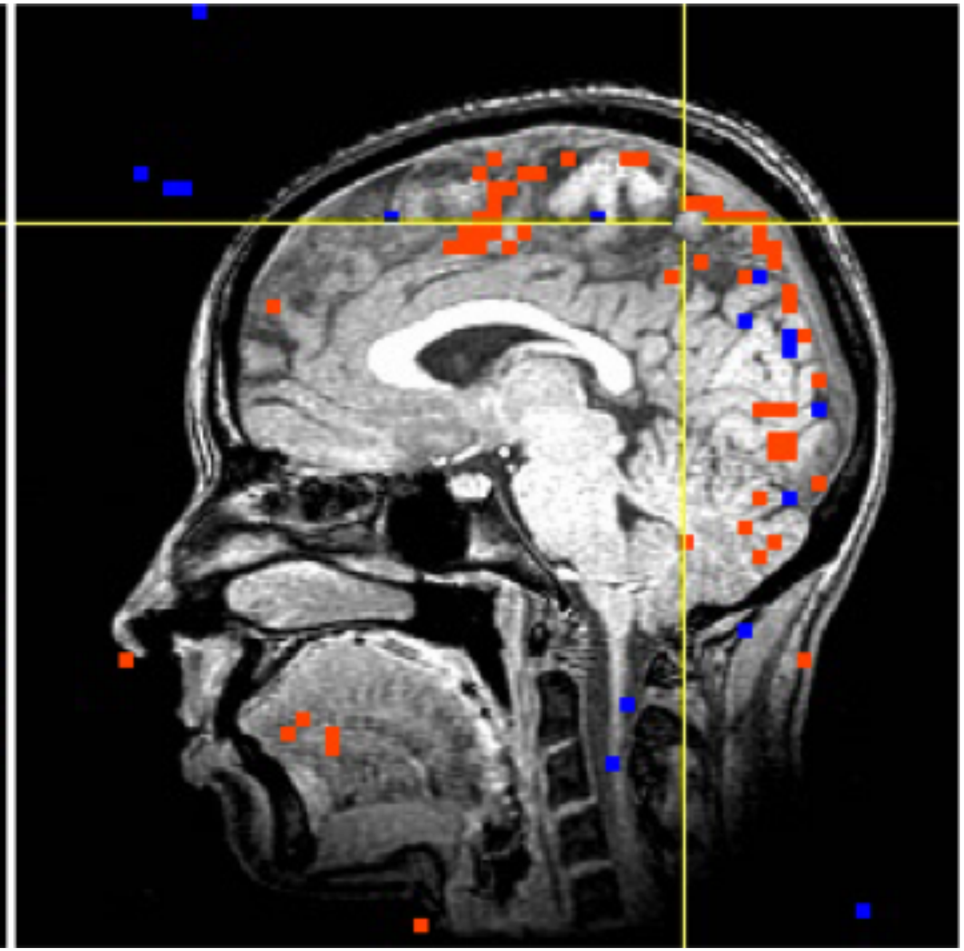
Linear Model with Fixed-Shape HRF

- FMRI data = baseline + drift + other effects of no interest + response1 + … + response$k$ + noise
- 'baseline' = **baseline** + **drift** + **other effects of no interest**
  - Drift: physiological effect, tiny motions, scanner fluctuations
  - Data = '**baseline**' + effects of interest + noise
  - **Baseline condition (and drift)** is treated in AFNI as **baseline model**, an additive effect, not an effect of interest (*cf.* **SPM/FSL**)
  - **Baseline+drift+**… also need parameters in the model fit
- $y_i = \alpha_0 + \alpha_1 t_i + \alpha_2 t_i^2 + \beta_1 x_{1i} + \ldots + \beta_k x_{ki} + \ldots + \varepsilon_i$ [i = time]
- $\mathbf{y} = \mathbf{X}\beta + \varepsilon$, $\mathbf{X} = [1, t, t^2, x_1, x_2, \ldots, x_k, \ldots]$ [vector format]
- In AFNI **baseline + slow drift** is modeled with polynomials
  - A longer run needs a higher order of polynomials
    - One polynomial order per 150 sec is the default in AFNI
  - With m>1 runs, m sets of polynomials needed to allow for temporal discontinuities across runs
    - $m(p+1)$ columns for **baseline+slow drift** with p-order polynomials
- Other effects of no interest: head movement estimates

Stimulus Correlated Motion = Bad



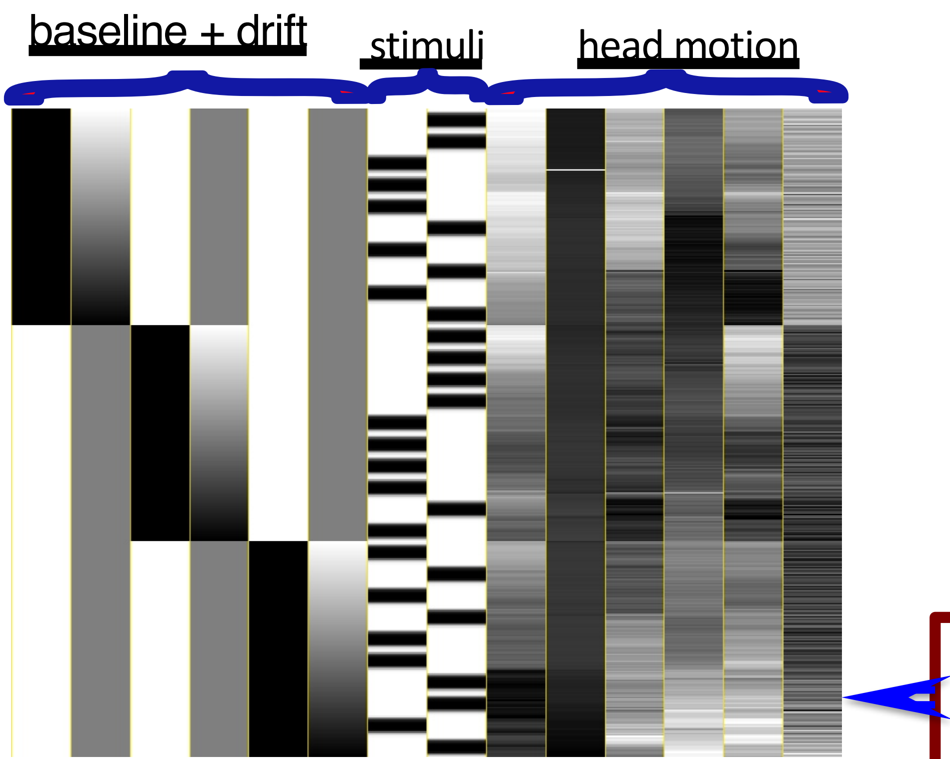
Activation map with image registration but *without* using movement estimates as regressors



Activation map when also using movement estimates as regressors

Design Matrix with Fixed-Shape HRF

- 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 $X = [1, t, x_1, x_2, \ldots, x_k, \ldots]$ in grayscale image

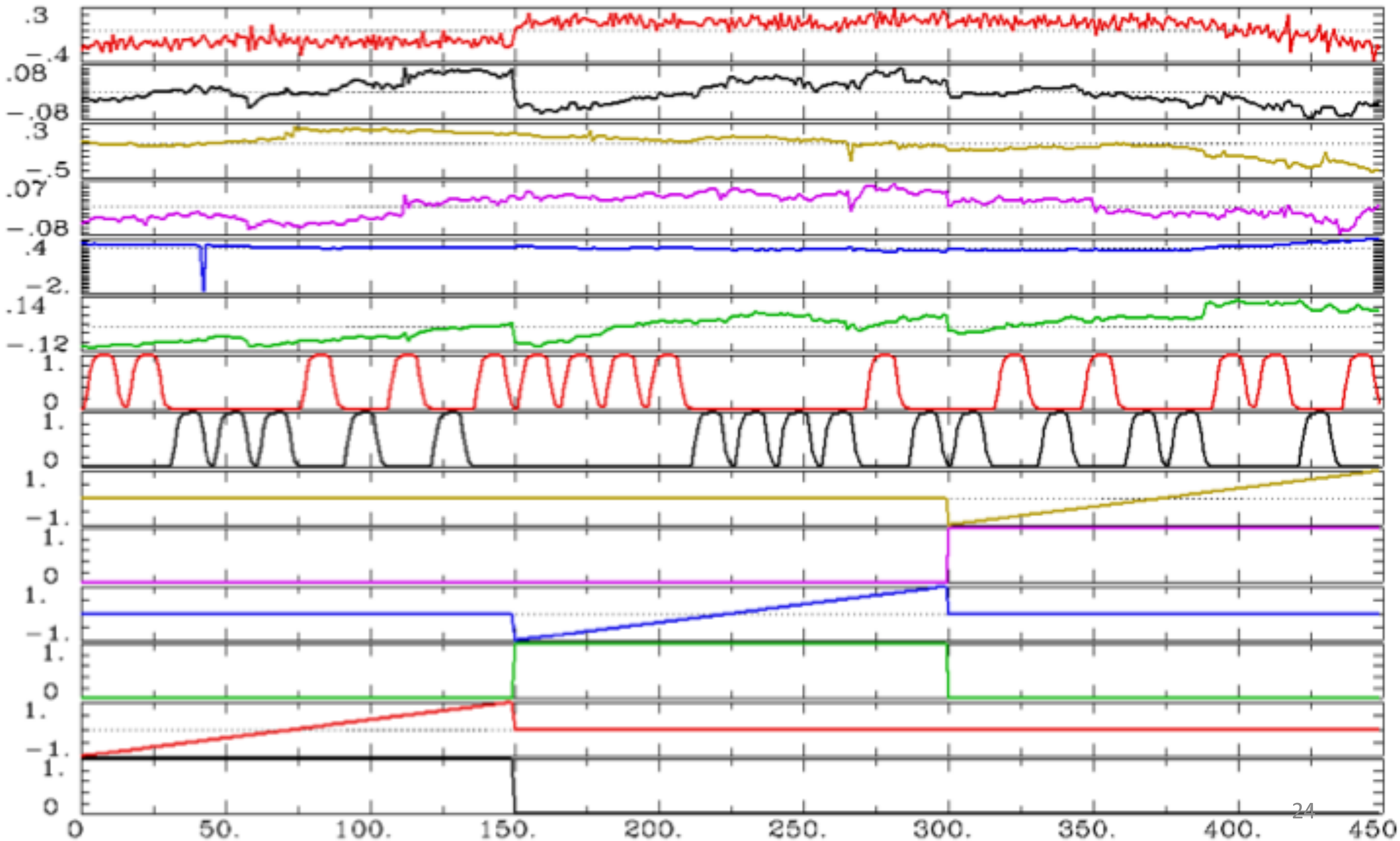


- 6 drift effect regressors
  - linear baseline
  - 3 runs x 2 parameters/run
- 2 regressors of interest
  - that is, relevant to brain activity
- 6 head motion regressors
  - 3 rotations + 3 shifts

Black = bigger numbers
White = smaller numbers
Each column of **X** scaled separately

Design Matrix with Fixed-Shape HRF

- Visualizing same design matrix $X = [1, t, x_1, x_2, \ldots, x_k, \ldots]$ in graphs



Assessing Fixed-Shape HRF Approach

- Used 99% of time: Why is it popular?
  - Assume brain responds with **same shape** across 4 levels: **subjects**, activated **regions**, stimulus **conditions/tasks**, **trials**
    - Difference in **magnitude** β in different conditions or different subjects (and its significance) is what we focus on
    - Strong assumption about **four** levels of shape information?
  - **Easy to handle and think about**: one value per effect/task
  - 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 responses overlap? Same effect across events?
- ***Not*** what you want if you
  - Care/worry about shape difference across subjects, across regions, across conditions, and across trials
  - Improved modeling

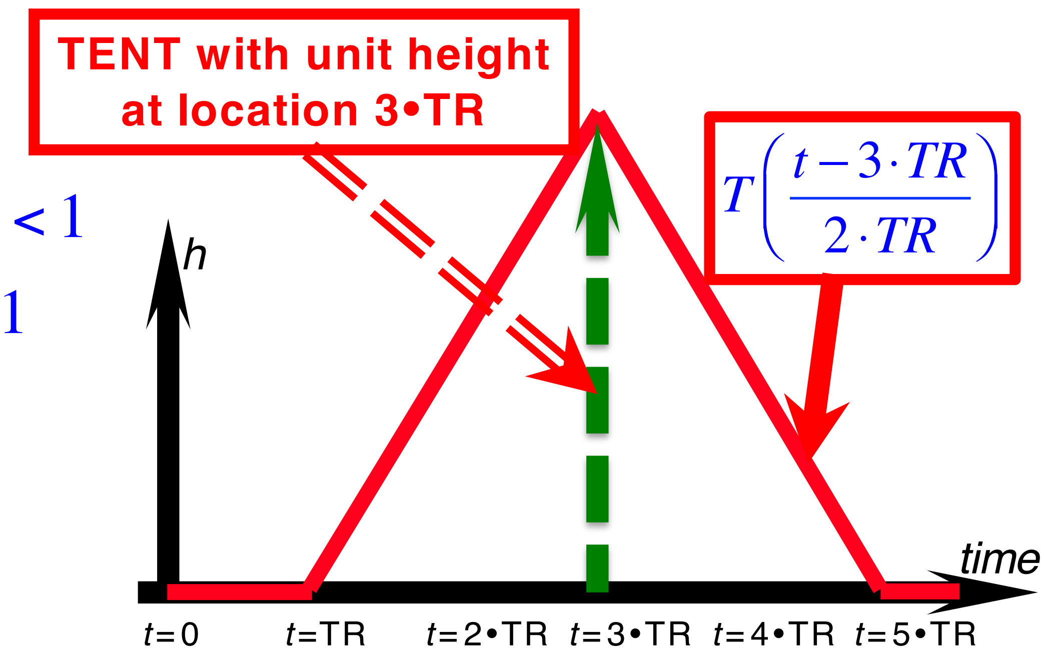
Alternative: No Constraint on HRF Shape

- TENT expansion of HRF
  - ➢ Set multiple tents at various equally-spaced locations to cover the potential BOLD response period
    - o Each TENT is a **basis function**
    - o HRF is a sum of multiple basis functions, each with its own β
  - ➢ BOLD response measured by TENT heights (βs) at all locations
  - ➢ TENTs are also known as 'piecewise linear splines'

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

Formula for standardized TENT centered at x=0, width=±1

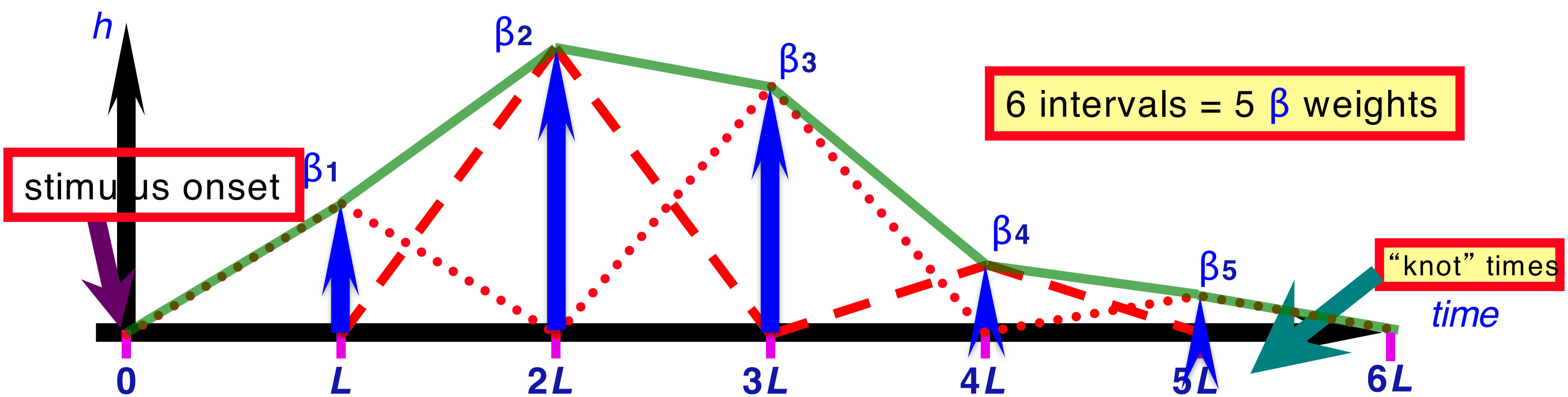
Cubic splines (CSPLIN) are also available in AFNI



Σ Tent Functions = Linear Interpolation

- 5 equally-spaced TENT functions = 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*** = **2*L*** 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 Functions Create the HRF

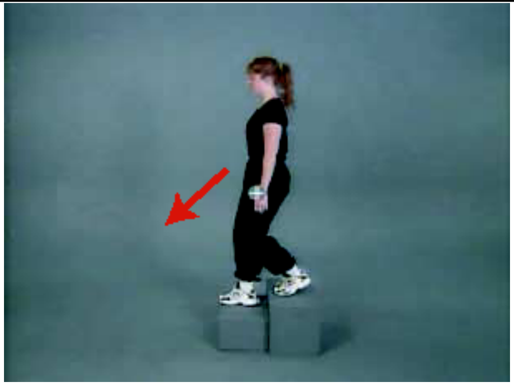
- And then the HRF is repeated for all stimuli of the same type
- In the example on the last slide, the HRF has 5 parameters (βs) to be estimated
- The βs determine the amplitude (percent signal change) ***and*** the shape of the HRF
- Each voxel in each subject gets a separate HRF shape now, not just a separate amplitude
  – And if there are multiple types of tasks, each task gets a separate shape
- Stimulus times do ***not*** have to be exactly on the TR grid

Modeling with TENTs - Example

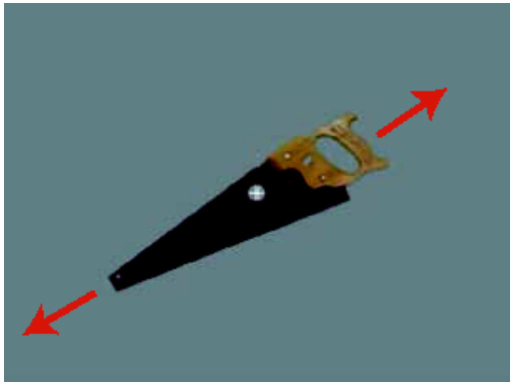
- Event-related study (Beauchamp et al., J Cogn Neurosci 15:991-1001)
  - 10 runs, 136 time points per run, TR=2 s
  - Two factors
    - Object type: **human** vs. **tool**
    - Object form in videos: **real image** vs. **points**
  - 4 types (2x2 design) of stimuli (short videos)
    - Tools moving (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**

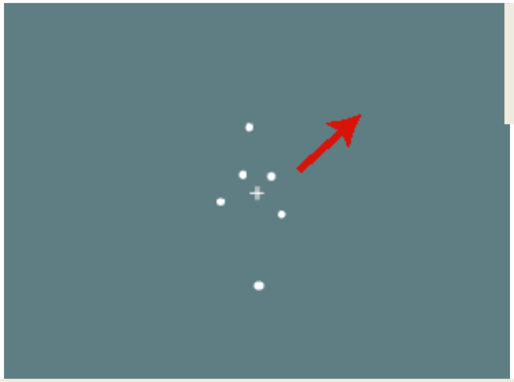
Human whole-body motion (HM)



Tool motion (TM)

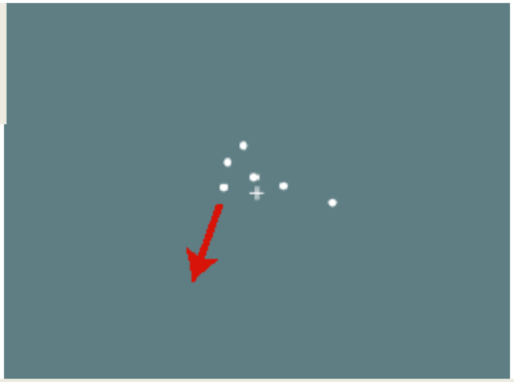


Human point motion (HP)



From Figure 1
Beauchamp et al. 2003

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?

Each video is only shown once (2 seconds)

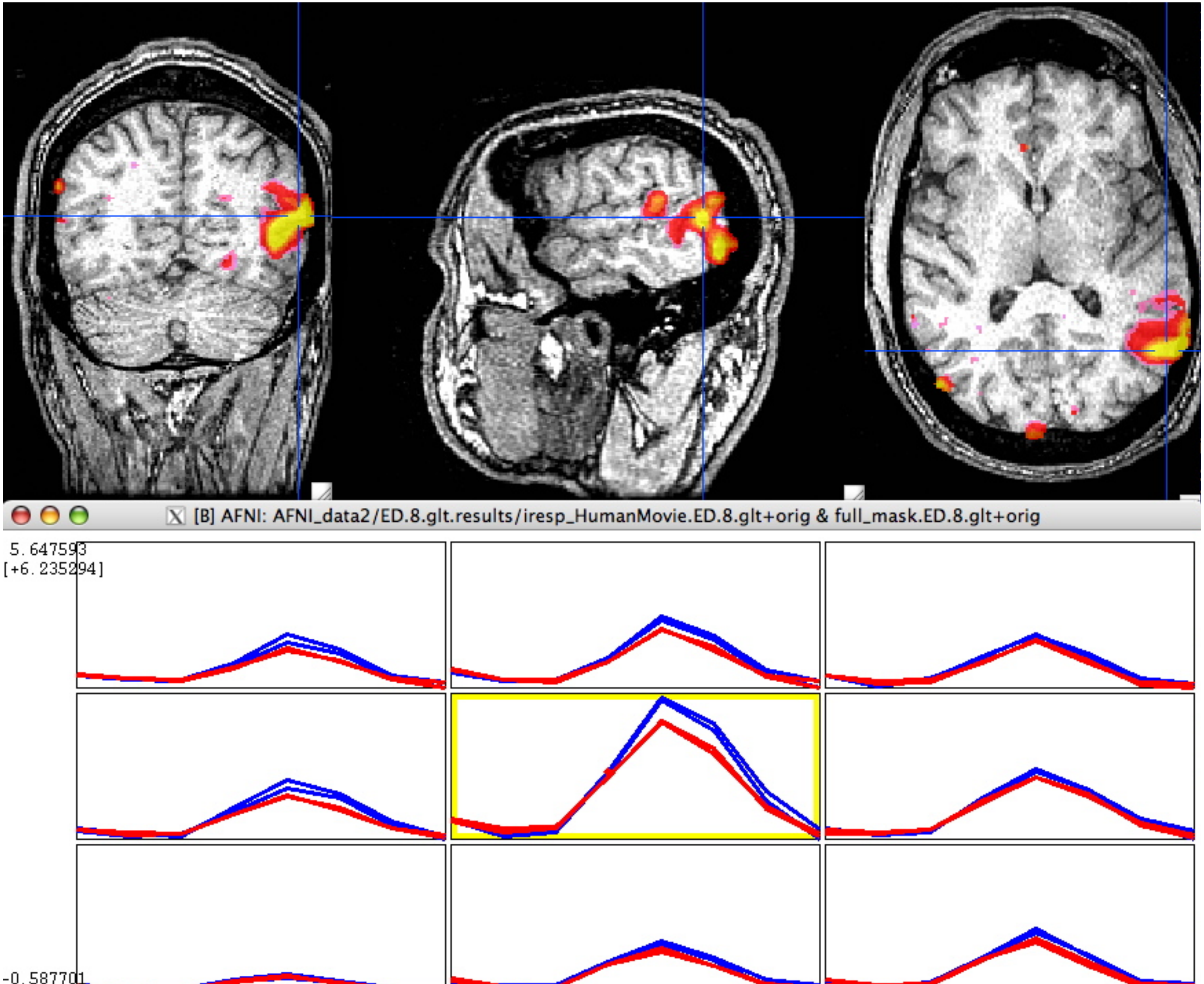
Design Matrix with **TENTzero(0,16,9)**

Baseline + quadratic trend for 10 runs

7 tents per condition × 4 conditions

head motion

Results: Humans vs. Tools



- Color overlay: **Human vs Tool ($\beta_{HM}+\beta_{HP}-\beta_{TM}-\beta_{TP}$)**
- **Blue** (upper) : Human
- **Red** (lower) : Tool

No Constraint on HRF Shape = **Deconvolution**

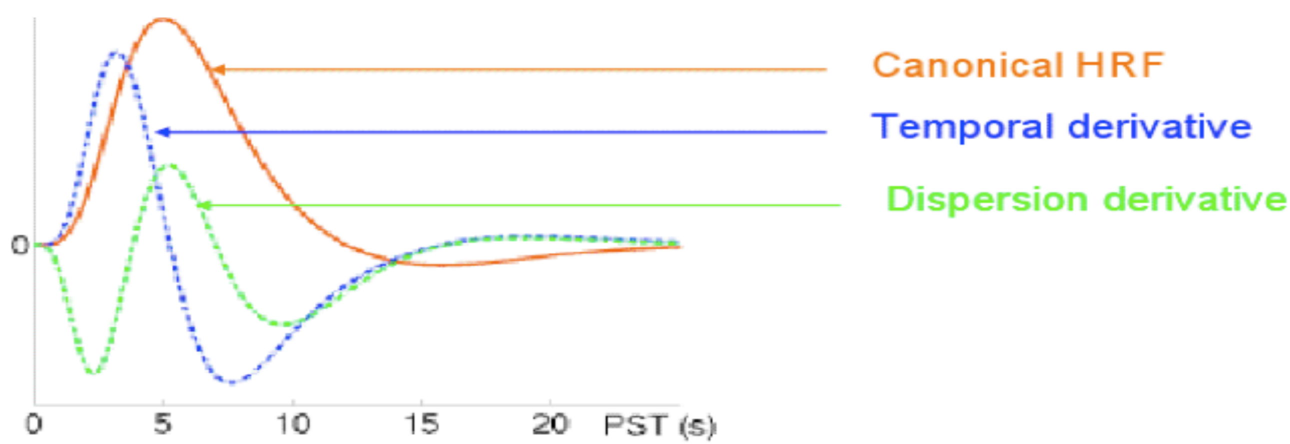
- Deconvolution perspectives: inverse process of convolution
  - ➢ HRF ⊗ stimulus = unit BOLD response
    - o Like multiplication, we have to know two and estimate the 3rd
  - ➢ Fixed-shape approach: Convolution + regression
    - o Known: HRF shape, stimulus
    - o Use convolution to create regressors (hidden from user inside 3dDeconvolve program)
    - o Response strength (β) estimated via linear model with programs 3dDeconvolve or 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 basis functions: TENTs
    - • Each TENT ⊗ stimulus = one regressor column
    - • Deconvolution: HRF = a set of βs estimated via regression

No Constraint on HRF Shape: Pros + Cons

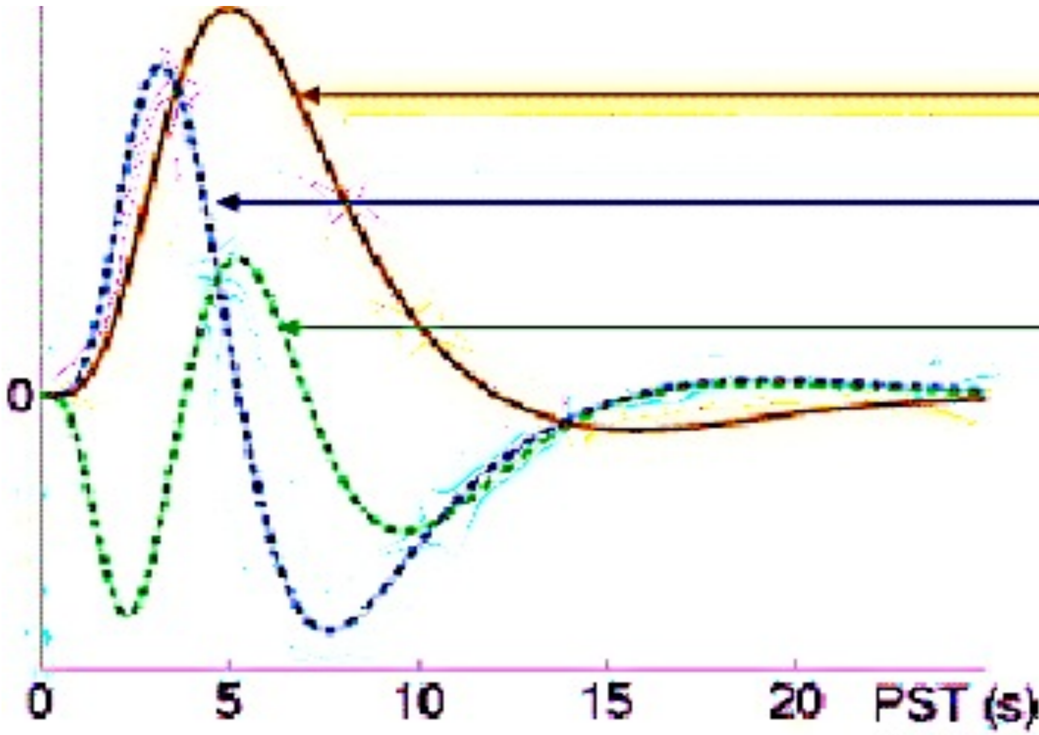
- What is the approach good at?
  - Usually for event-related experiments, but can be used for BLOCK
    - Multiple basis functions for blocks: within-block attenuation with time
  - Likely to have more accurate estimate on HDR shape across
    - subject
    - conditions/tasks
    - brain regions
  - Likely to have better model fit (the goal in the sample experiment)
  - 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 [see the program 3dMVM]
    - Multiple parameters (βs) per task condition, instead of just one
  - More regressors than alternatives: DoF's per subject
  - Risk of highly correlated regressors: Multicollinearity
    - May need to reduce the number of basis functions
  - Over-fitting: picking up something (head motion) unrelated to HDR

Intermediate Approach: SPMG1/2/3

- Use just a few 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 width



SPMG1/2/3
[Ready for their closeup, Mr. DeMille]



- You can use these as basis functions in AFNI
- We don't usually recommend this
- The next few talks show the details of how to choose the basis functions for the HRF

Multicollinearity

- Voxel-wise regression model: $y = \mathbf{X}\beta+\varepsilon$
  - ➢ Regressors in design matrix $\mathbf{X}$ = $[1, t, t^2, x1, x2, \ldots, xk, \ldots]$
- Multicollinearity problem
  - ➢ Two or more regressors highly correlated
  - ➢ Difficult or impossible to distinguish the effects among these regressors (*i.e.*, get reliable β estimates)
- Multicollearity scenarios
  - ➢ Collinearity - $x_i = \lambda x_j$ = model specification error; *e.g.*, 2 identical regressors (mistake in stimulus timing specifications)
  - ➢ Exact multicollinearity: linear dependence among multiple regressors = faulty design (rare)
  - ➢ High degree of correlation (+ or -) among regressors = design problem (*e.g.*, cue + movie watching)
  - ➢ Too many basis functions in response model
- Diagnosis tools: ExamineXmat.R, timing_tool.py, xmat_tool.py

Serial Correlation in Residuals

- Why temporal correlation?
  - In the residuals/noise (not the time series data)
  - Short-term physiological effects (breathing, heartbeat)
  - Other unknown reasons (scanner issues?)
- What is the impact of temporal correlation?
  - With white noise assumption, βs are unbiased, but the statistics tend to be inflated
  - Little impact on group analysis – if only using βs from subjects
  - May affect group analysis if considering effect reliability, as in AFNI's 3dMEMA program (where βs and ts are used)
- Approach in AFNI
  - ARMA(1,1) noise model for residual time series correlation
  - Slightly different from other packages:
    - Serial correlation model is computed voxelwise, not globally
  - Described in the Advanced Regression talk: 3dREMLfit

Dealing with Multiple Runs per Subject

- Possible approaches
  - Analyze each run separately: AFNI, FSL
    - Have to have enough task repetitions per run
    - Can test cross-run difference (trend, habituation) at group level
    - Usually need to 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
    - Still need to summarize multiple β's before group analysis
  - Concatenate but analyze with same regressor across runs for each condition type: default in AFNI
    - Assumes no attenuation across runs
- Cross-block (or cross-event) attenuation
    - Method: IM or AM regression models
    - *cf*. Advanced Regression talk

Percent Signal Change

- Why conversion/scaling for %? Comparable across subjects
  - MRI and BOLD data values don't have any useful physical/physiological meaning
  - Baseline is different across subjects (and possibly scaling)
  - It's the relative changes that can be compared across subjects
- AFNI approach
  - Pre-processing: data scaled by **voxelwise** mean
    - % signal change relative to **mean**, not exactly to **base**line
      - Difference is tiny: less than 5% (since BOLD effect is small)
  - 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 desired

Lackluster Performance in Modeling

- **Essentially, all models are wrong, but some are useful** (G.E.P. Box)
- Noisy data: too easy excuse!
- Regressors: idealized response model
  - We find what we're looking for
  - We may miss something when we fail to look for it
- Lots of variability across trials (response and noise)
  - **A**mplitude **M**odulation if behavioral data are available
  - Model each trial separately (**I**ndividual **M**odulation)
- 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 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) or CSPLIN(b,c,n)
- Modeling with one major IRF plus shape adjustment
  - SPMG1/2/3
- Other issues
  - Multicollinearity
  - Catenation
  - Percent signal change