FMRI Task-Based Data Analysis at the Individual Level

SSCC/NIMH/NIH/DHHS/USA/Earth

FMRI data analysis: The Big Picture

Four stages

- Experimental design & data collection
- Preprocessing & quality control
- Modeling
  - Individual level
  - Population level
- Result reporting

Modeling goals

- Statistical inference: relationship estimation
  - Causal effects: task-based FMRI
  - Correlations: resting state FMRI
- Prediction

Statistical inference goals

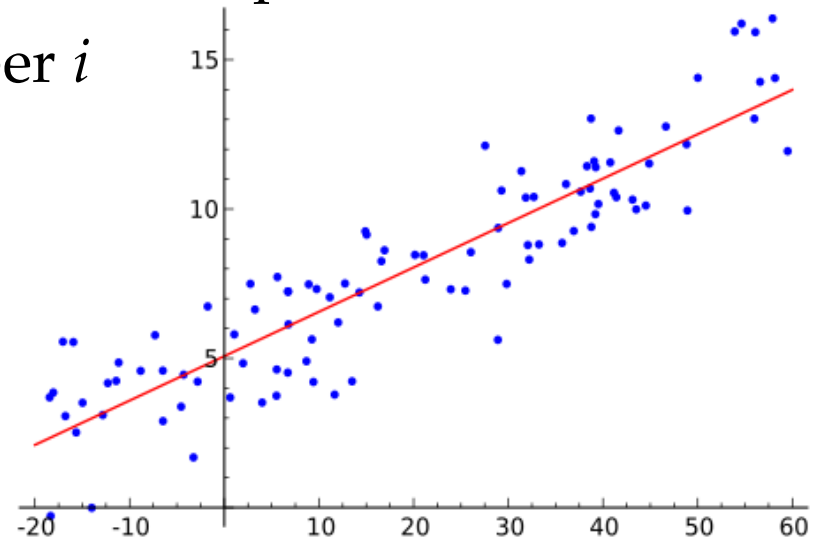
- Localization: task → regional BOLD responses
- Network level: cross-regional associations
  - Remember: *correlation does not imply causation*

Overview

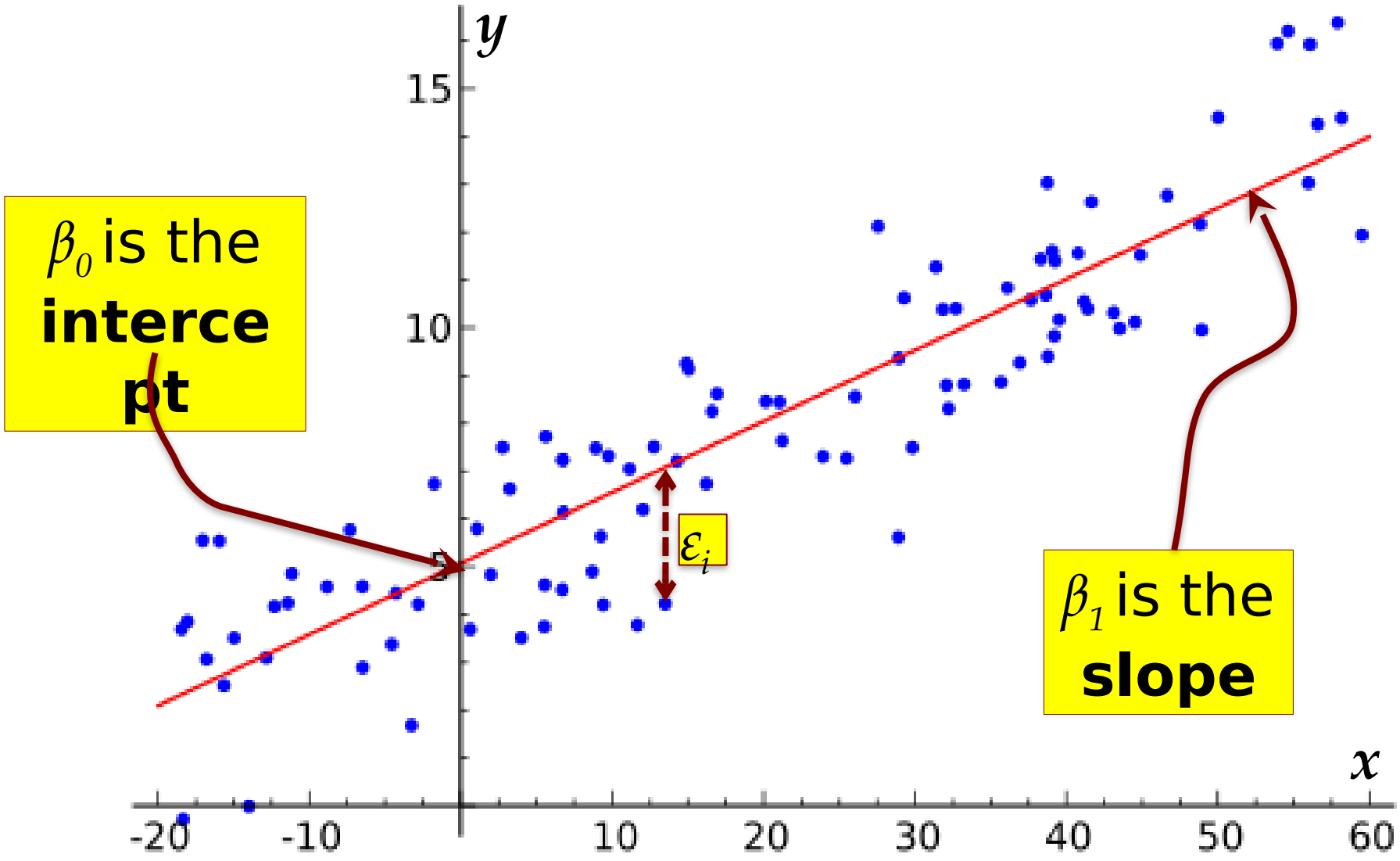
- Basics of linear models for data analysis
- FMRI data decomposition: three components
  - **Baseline + slow drift + effects of no interest**; **Effects of interest**; **Noise**
  - Effects of interest – understanding BOLD vs. stimulus
    - IRF and HRF and HDR
- Three modeling strategies
  - Fixed-shape 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**)

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

- 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** $\boldsymbol{\beta}$ (and statistics about $\boldsymbol{\beta}$)
- 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 $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$
  - "Project" data **y** onto the space of explanatory variables (**X**)
  - **OLS** formula for solution: $\hat{\boldsymbol{\beta}} = (\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{y}$
  - 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**

Linear regression sidenote

$$\mathbf{y} = B_0\mathbf{1} + B_1\mathbf{x_1} + B_2\mathbf{x_2} + B_3\mathbf{x_3} + B_4\mathbf{x_4} + \ldots + \boldsymbol{\varepsilon}$$

Regression modeling or GLM:

- We state that:
  - a time series **y** *can be* expressed as the sum of many components $\mathbf{x}_i$ (AKA the regressors, terms, effects, …)
  - **bold** quantities are time series (1D vectors; even a vector of 1s), and others are scalar (numbers)
- We choose (!) what those important features are
  - some mathematical constraints apply on building a model
- Task-based FMRI and resting state/naturalistic FMRI focus on different model features
  - estimate uncertainty can/should be included

Linear regression sidenote

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"input" data: what we want to model, and study one or more features or components

regressors of no interest: useful time series ($\mathbf{x}_i$), but don't care about their effect size (B_i)

regressors of interest: useful time series ($\mathbf{x}_i$), and yes we do care about their effect size (B_i)

residual (or "error") time series: everything "else" from **y** that is not explicitly modeled by components ($\mathbf{x}_i$), and sometimes used or ignored

Linear regression sidenote

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e.g.

- baseline modeling and drift, via low freq sinusoids or polynoms
- time series of estimated subject motion (esp. catch spikes)
- time series from non-GM, to capture other motion aspects
- physiological regressors, from respiration and/or heart

Linear regression sidenote

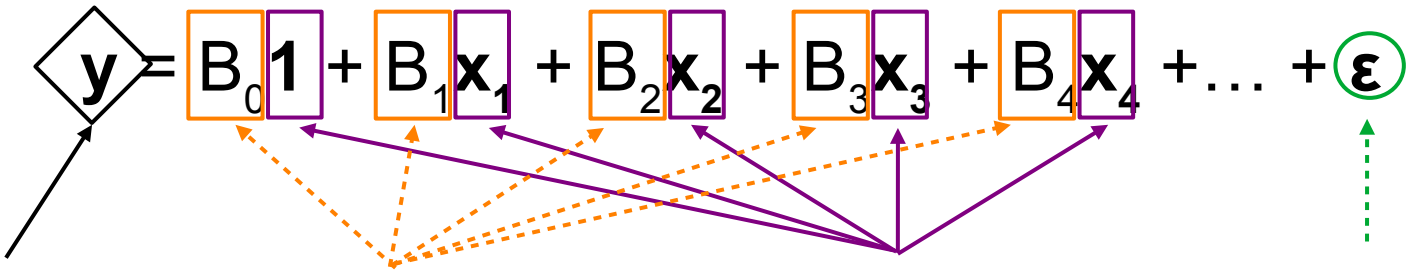
$$\underbrace{y}_{\text{“input” data: what we want to model, and study one or more features or components}} = \underbrace{B_0 1 + B_1 x_1 + B_2 x_2}_{\text{regressors of no interest: useful time series } (x_i), \text{ but don't care about their effect size } (B_i)} + \underbrace{B_3 x_3 + B_4 x_4}_{\text{regressors of interest: useful time series } (x_i), \text{ and yes we do care about their effect size}} + \ldots \underbrace{+ \varepsilon}_{\text{residual (or “error”) time series: everything “else” from } y \text{ that is not explicitly modeled by components } (x_i),}$$

NB:

In <u>task FMRI:</u> focus on regressors of interest and analyze their B_i (and uncertainties)

In <u>rest/naturalistic FMRI:</u> only model regressors are those of no interest, and we focus on the residuals for later analysis

Linear regression sidenote



known from the start

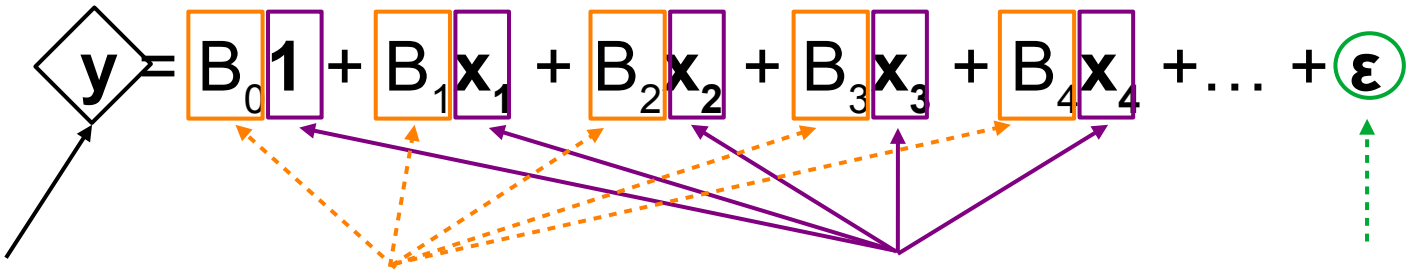
to be estimated via modeling (along with an uncertainty or standard error value)

created by the researcher, as the "model" or "design matrix", via theory, experience, experimental setup, literature, etc.

$\mathbf{X} = [1 \ x_1 \ x_2 \ x_3 \ x_4 \ ...]$

to be estimated in modeling process, as "leftover" from input after modeling

Linear regression sidenote



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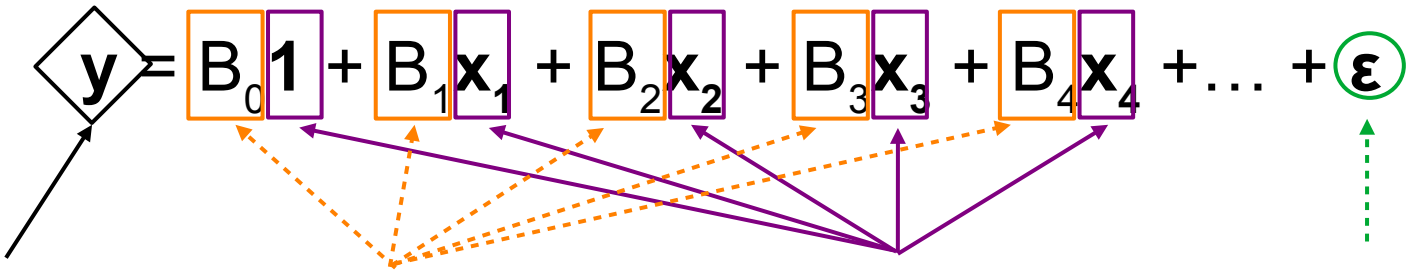
Comment on estimates:

For each regressor, we get two important quantities:

- $\hat{B}_i$: a coefficient, weight or effect size estimate for that term; it can have useful units, like BOLD % signal change, if **y** and the regressors are well-scaled
- t_i: a t-statistic for the coefficient, which is related to the estimated standard error $\hat{\sigma}_i = \hat{B}_i / t_i$; it provides uncertainty information for the estimate (and can be translated to significance, knowing the stat's degrees of freedom)

Linear regression sidenote



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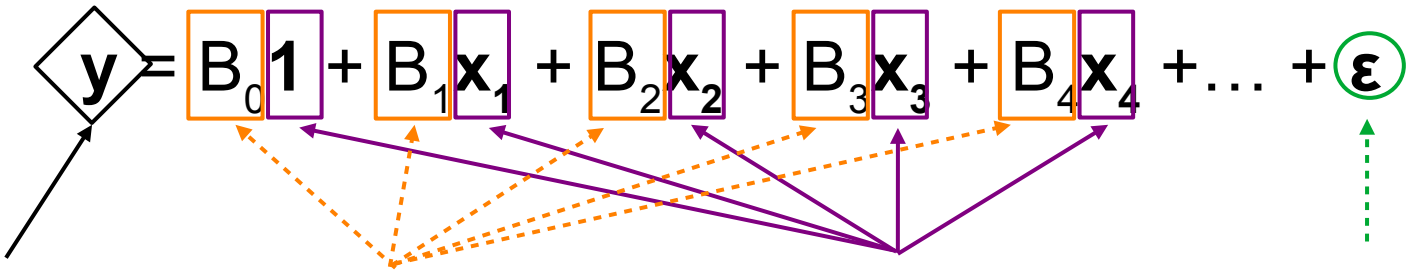
to be estimated in modeling process, as "leftover" from input after modeling

X-matrix considerations:

- In task FMRI, we want to avoid having regressors of interest *too similar to any combination of each other or regressors of no interest* ("collinearity")
  - If that happens, the effect estimate $\hat{B}_i$ is not valid or useful
  - Several other design features impact quality of $\hat{B}_i$ estimation

Linear regression sidenote



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X-matrix considerations:

- In rest/naturalistic FMRI, we include as many effects and features as might be useful, *but* we pay by using up degrees of freedom (DFs)
  - If **y** has *N* time points, then we start with *N* DFs
  - Each **regressor** in the design matrix uses up 1 DF from the final number held by the residual: fewer final DFs → greater uncertainty

Linear regression sidenote

$$\mathbf{y} = B_0\mathbf{1} + B_1\mathbf{x}_1 + B_2\mathbf{x}_2 + B_3\mathbf{x}_3 + B_4\mathbf{x}_4 + \ldots + \boldsymbol{\varepsilon}$$

The sum of the regressors and their estimated weights (so, the RHS *excluding* the residuals) is called the *fit time series*, which is also the modeled estimate of the input:

$$\hat{\mathbf{y}} = \hat{B}_0\mathbf{1} + \hat{B}_1\mathbf{x}_1 + \hat{B}_2\mathbf{x}_2 + \hat{B}_3\mathbf{x}_3 + B_4\mathbf{x}_4 + \ldots$$

Then, by definition:

y = (fit time series) + (residual or error time series)

We can use the *F*-statistic or coefficient of determination R^2 to estimate the relative variance of y that is explained within the model---that is, approximately how well our design matrix models the original input.

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

$$H_0: \beta_3 = 0$$

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

$$H_0: \beta_3 - \beta_5 = 0$$

$$H_0: 0.5*(\beta_3 + \beta_4) - \beta_5 = 0$$

  - *F*-test for <u>composite</u> null hypothesis

$$H_0: \beta_3 = \beta_4 = \beta_5$$

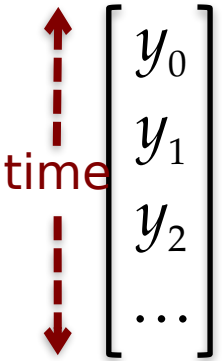
$$H_0: \beta_3 = \beta_4 = \beta_5 = 0$$

  - <u>Omnibus</u> or Full *F*-test for the entire model

$$H_0: \text{all } \beta_i \text{ values } \underline{\text{of interest}} \text{ are } 0$$

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 Experiment Terminology

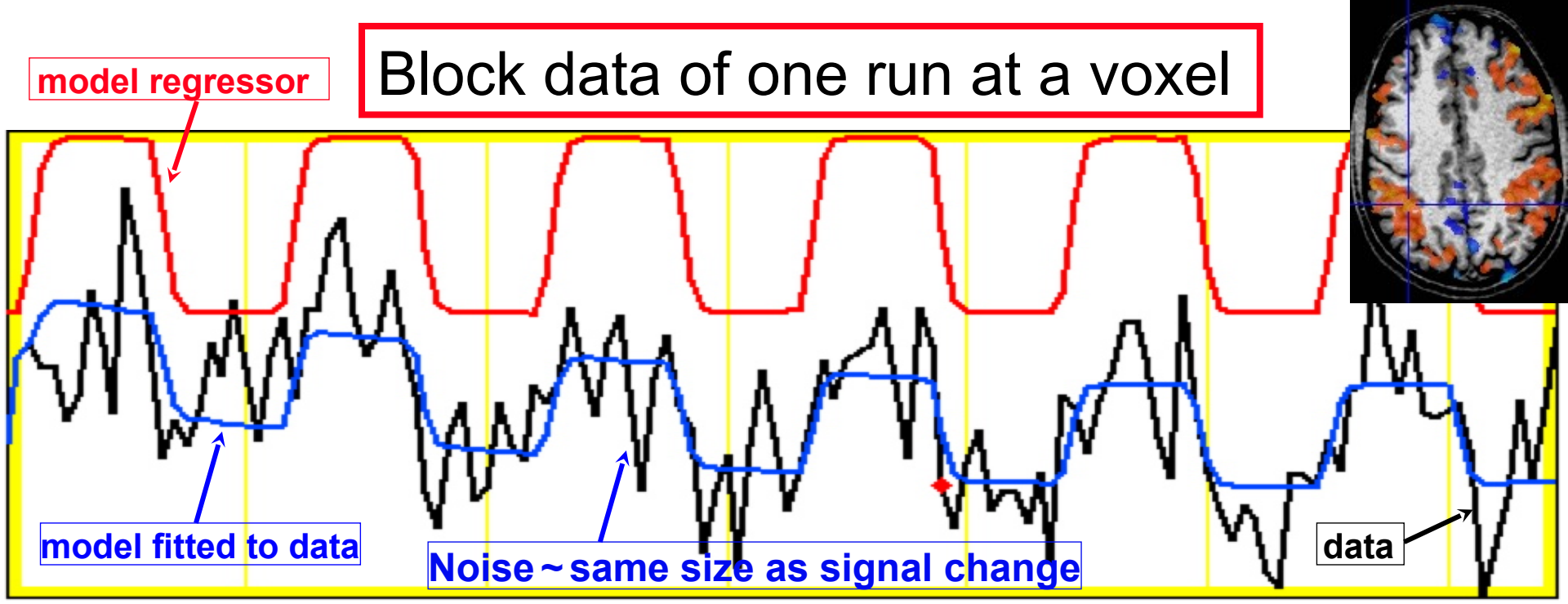
- Experiment setup
  - Number of subjects
  - Number of conditions [tasks, stimulus (trial, event) types]: Factorial design?
  - Sample size (repetitions) per condition
  - Block, event-related, or mixed?
  - Inter-stimulus interval (ISI) – regular, random?
- Scanning parameters: TR, voxel size, data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

Types of FMRI Experiments

- Two classical types of experiment design
  - **Block** (boxcar) design
    - Each stimulus 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
- Continuous stimulation (*e.g.*, movie watching)
  - Not covered here – more like resting state analysis

FMRI Data

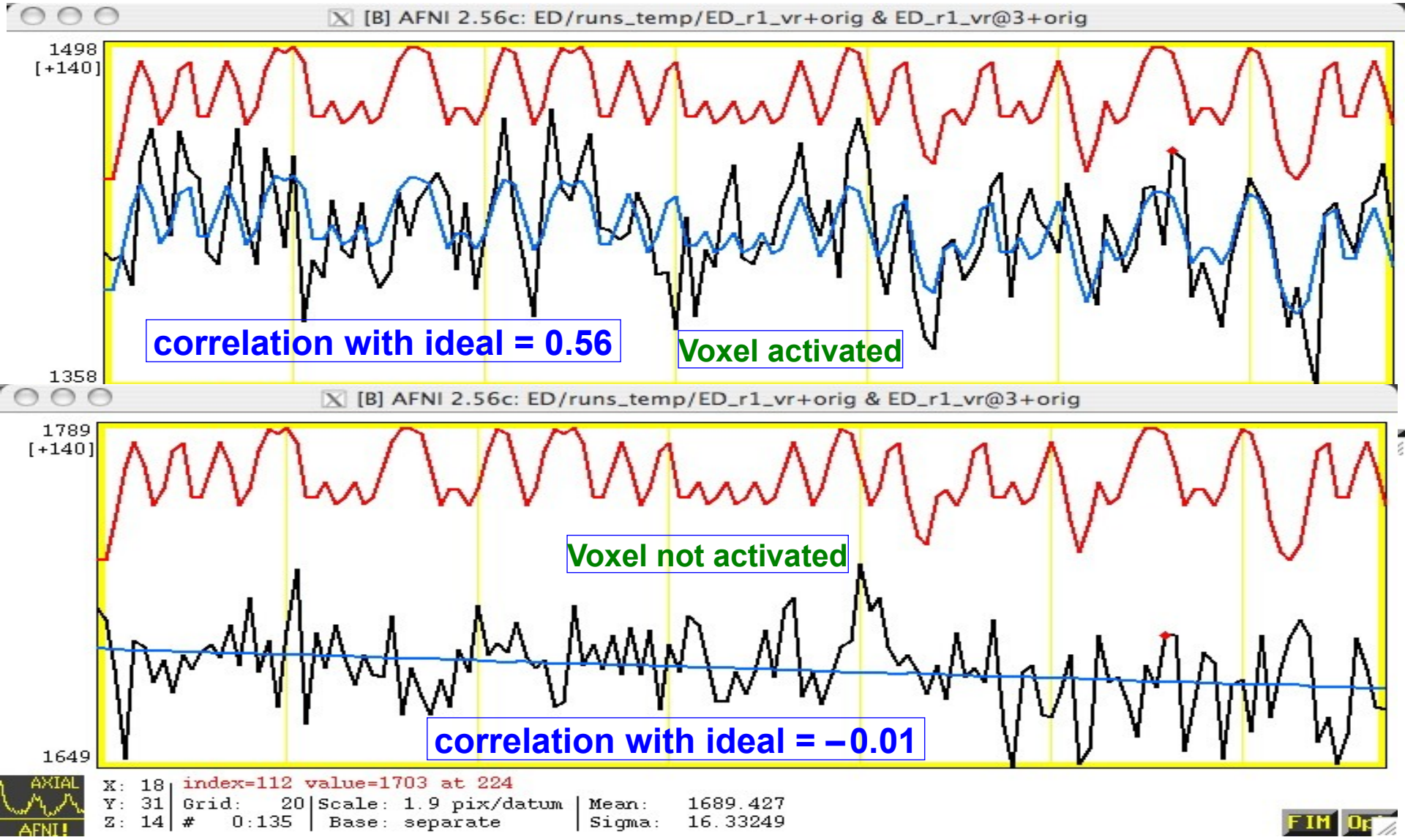
- Data partition: **Data = Signal + Noise**
  - **Data** = acquisition from scanner (voxel-wise time series)
  - **Signal** = BOLD response to stimulus; effects of interest + no interest
    - **We don't actually know the real signal shape to look for!!!**
    - Look for idealized task responses by assuming 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: 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?

Event-Related Data at 2 Voxels



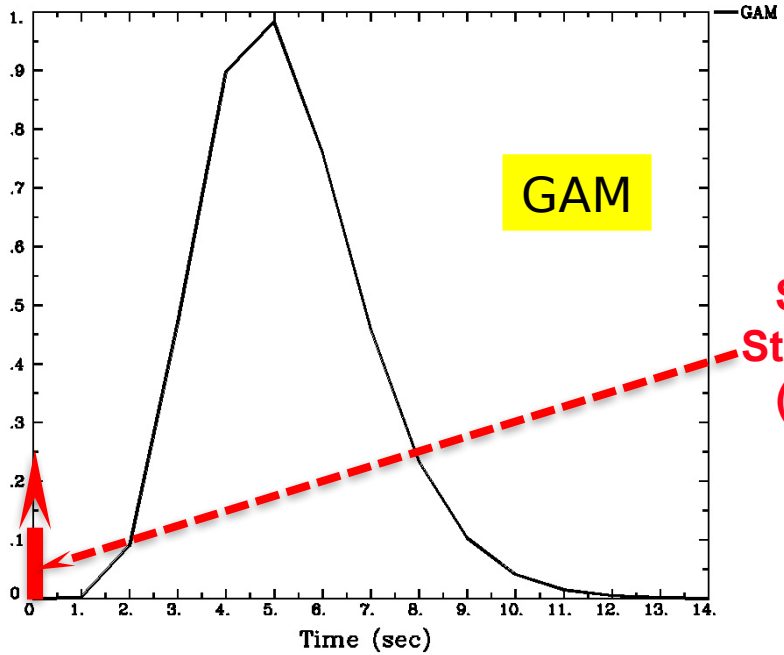
Lesson: ER-FMRI activation is not obvious via casual inspection

BOLD Response

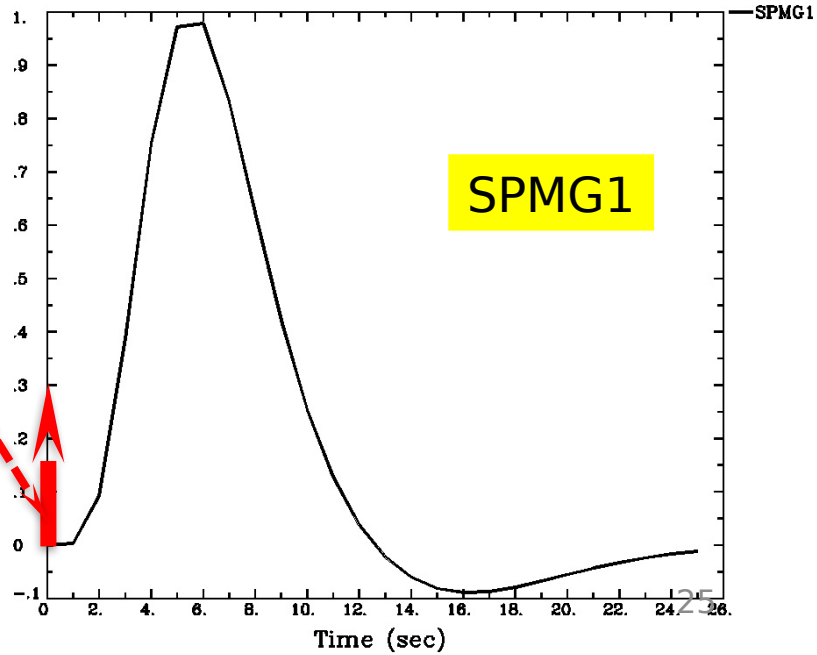
- Hemodynamic response (**HDR**)
  - Brain+FMRI response to stimulus/task/condition
  - Indirect measure of neural response: brain activation changes in blood oxygen changes in FMRI signal
- Hemodynamic response function (**HRF**)
  - Mathematical formulation/idealization of HDR for ***one*** full stimulus 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 $S(t)$: $x(t) = h(t) \otimes S(t)$

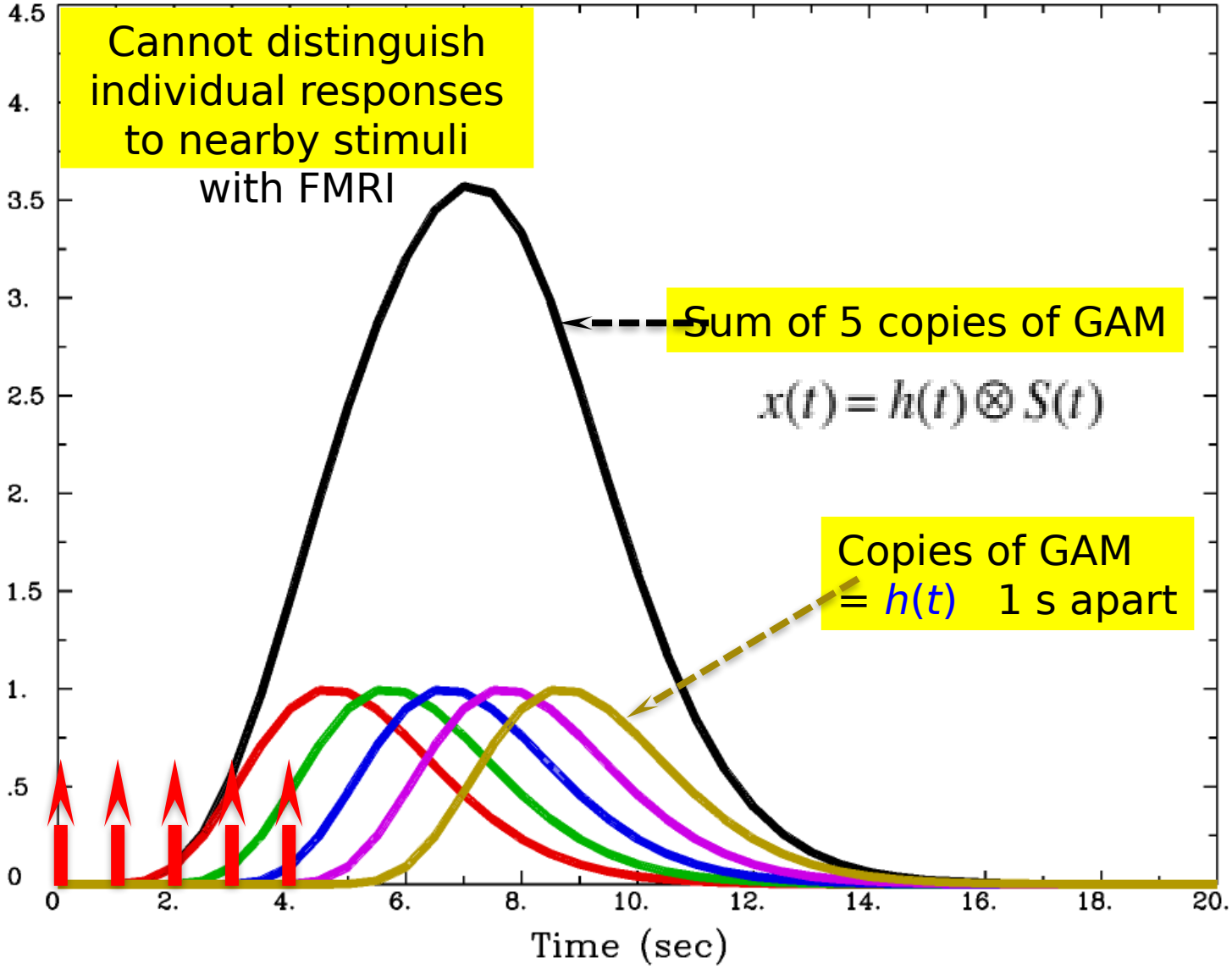


Short Stimulus (≤ 1s)



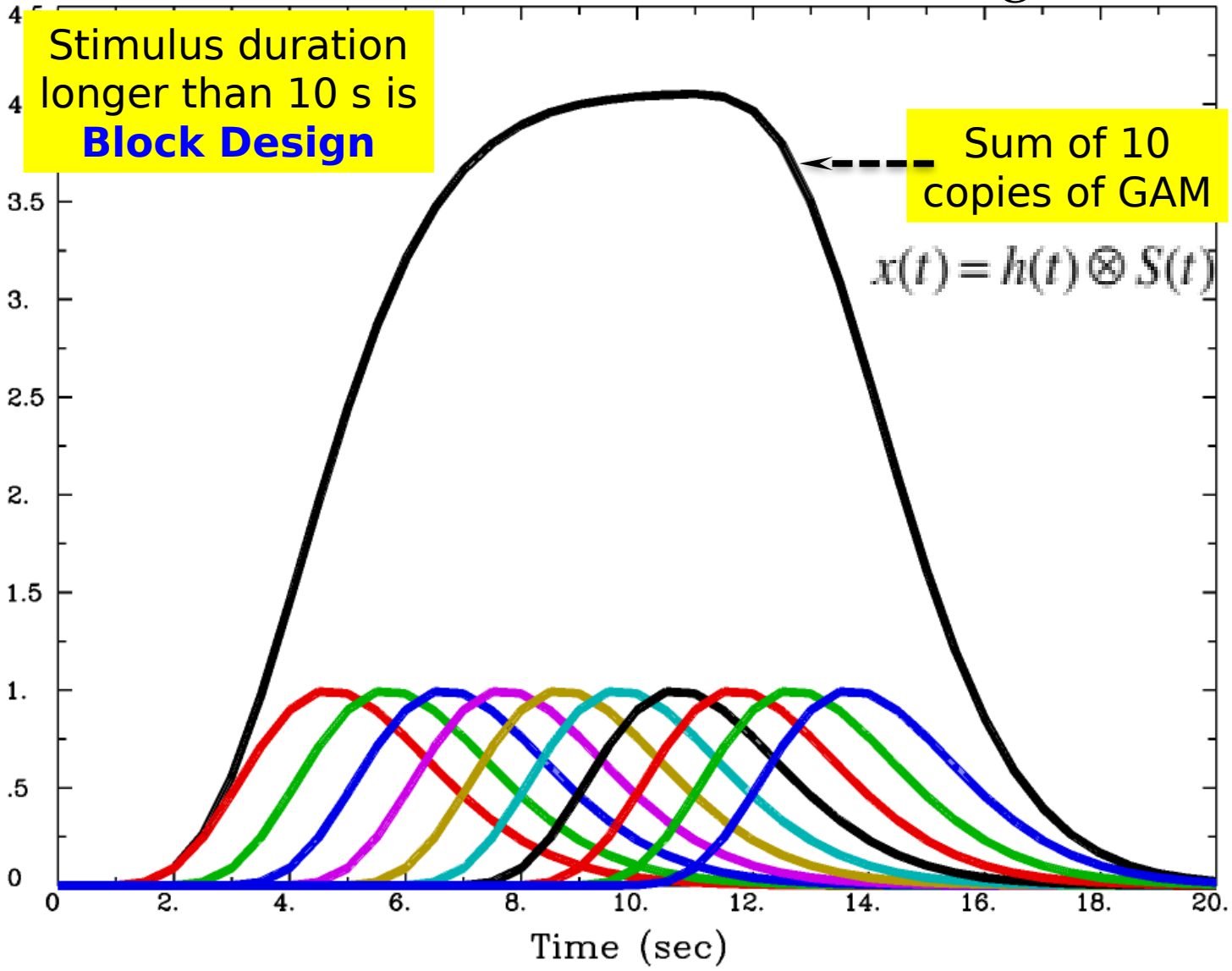
Fixed-Shape HRF – 5 s Stimulus

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



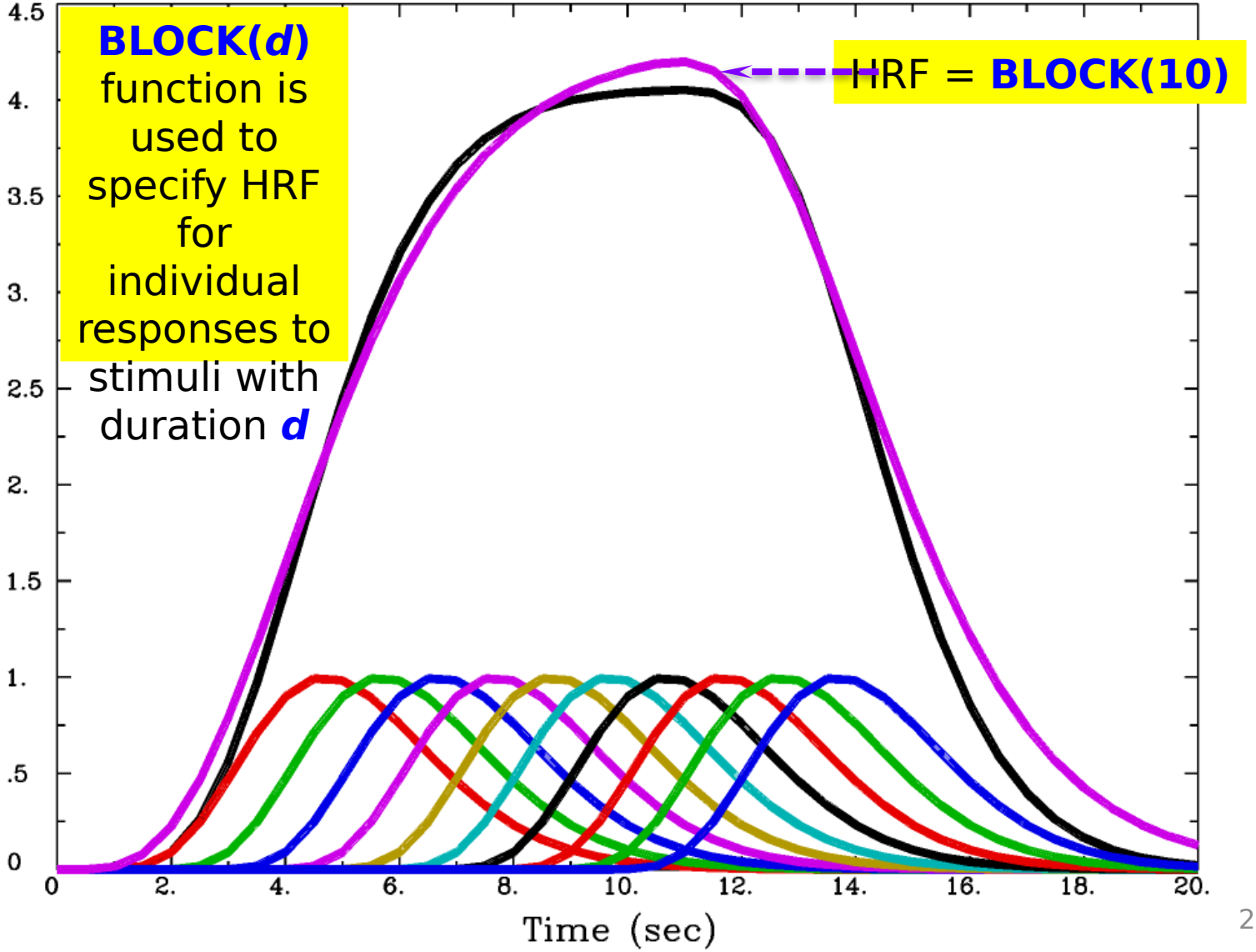
Fixed-Shape HRF – 10 s Stimulus

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



Fixed-Shape HRF – 10 s Stimulus

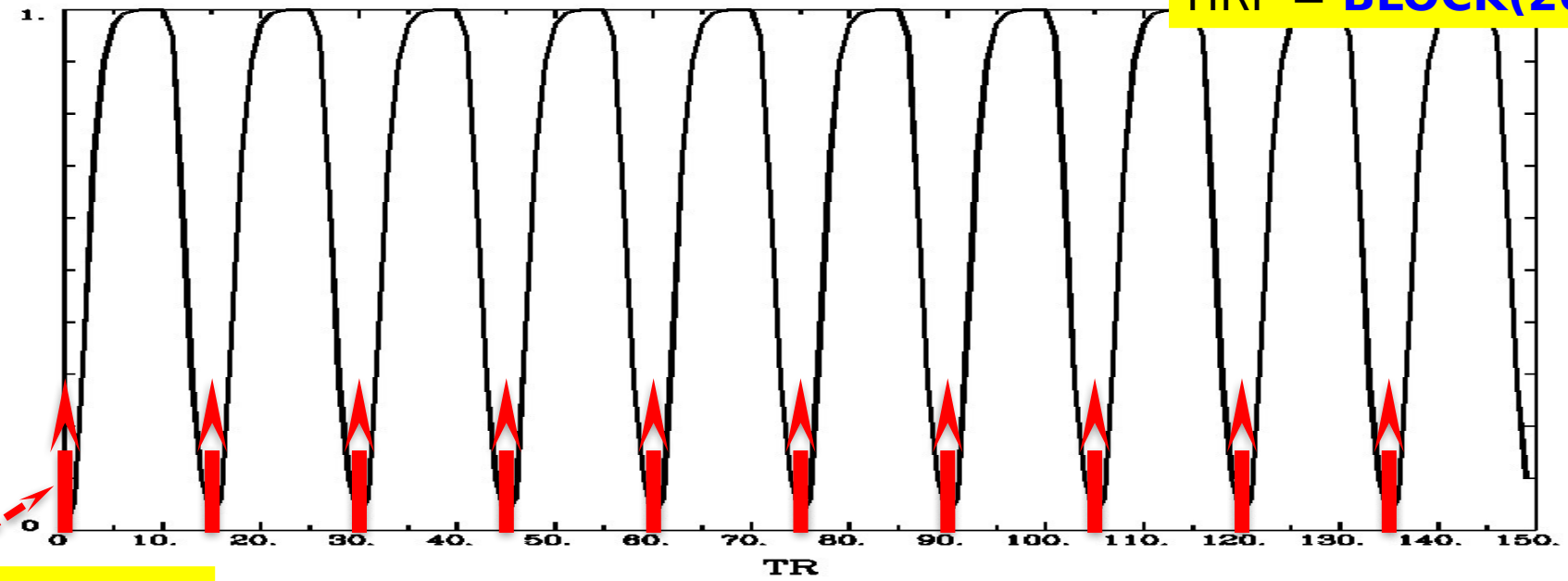
- With the '**BLOCK(10)**' function in AFNI



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)**

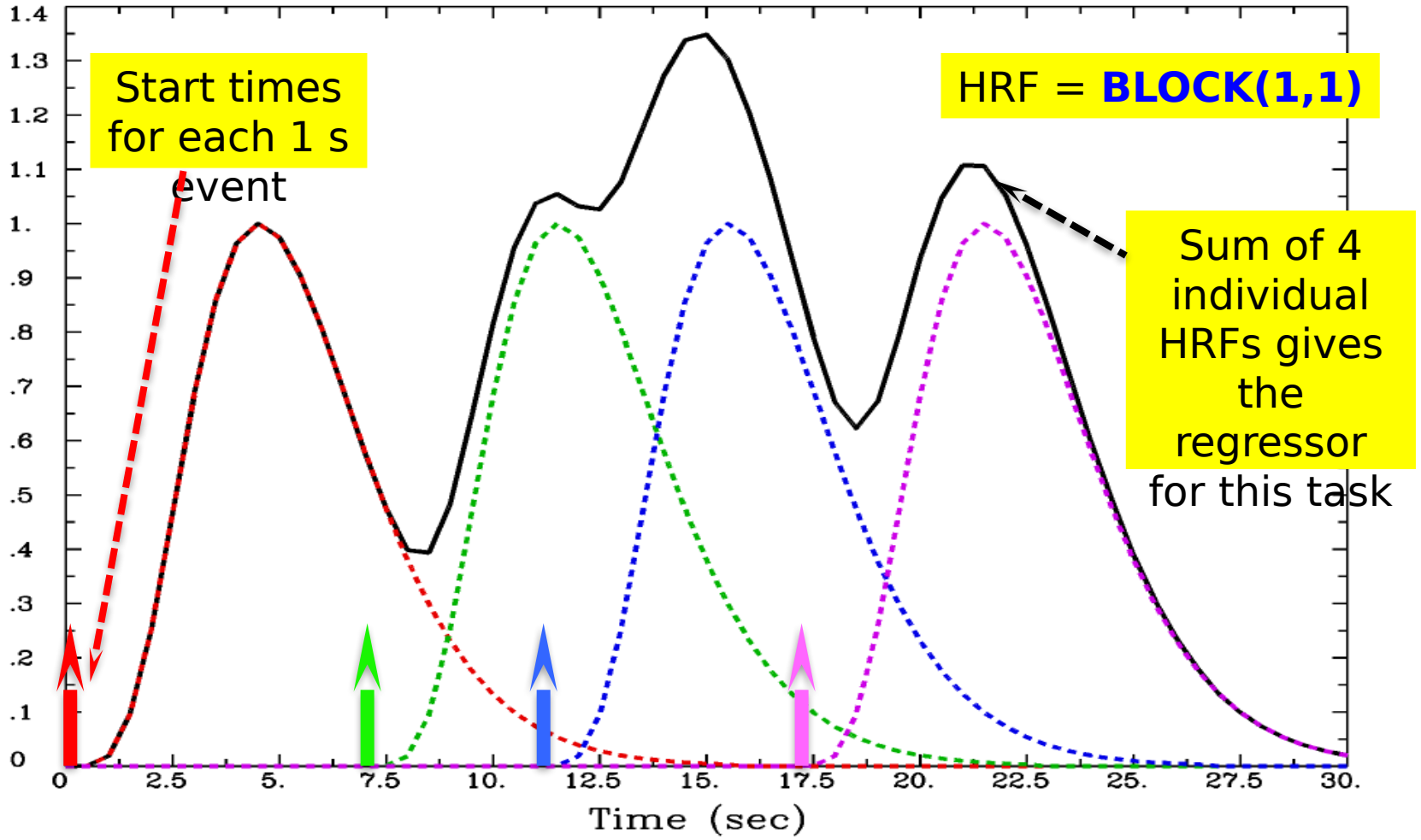


Start times for each block

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

Fixed-Shape HRF for Event-Related Design

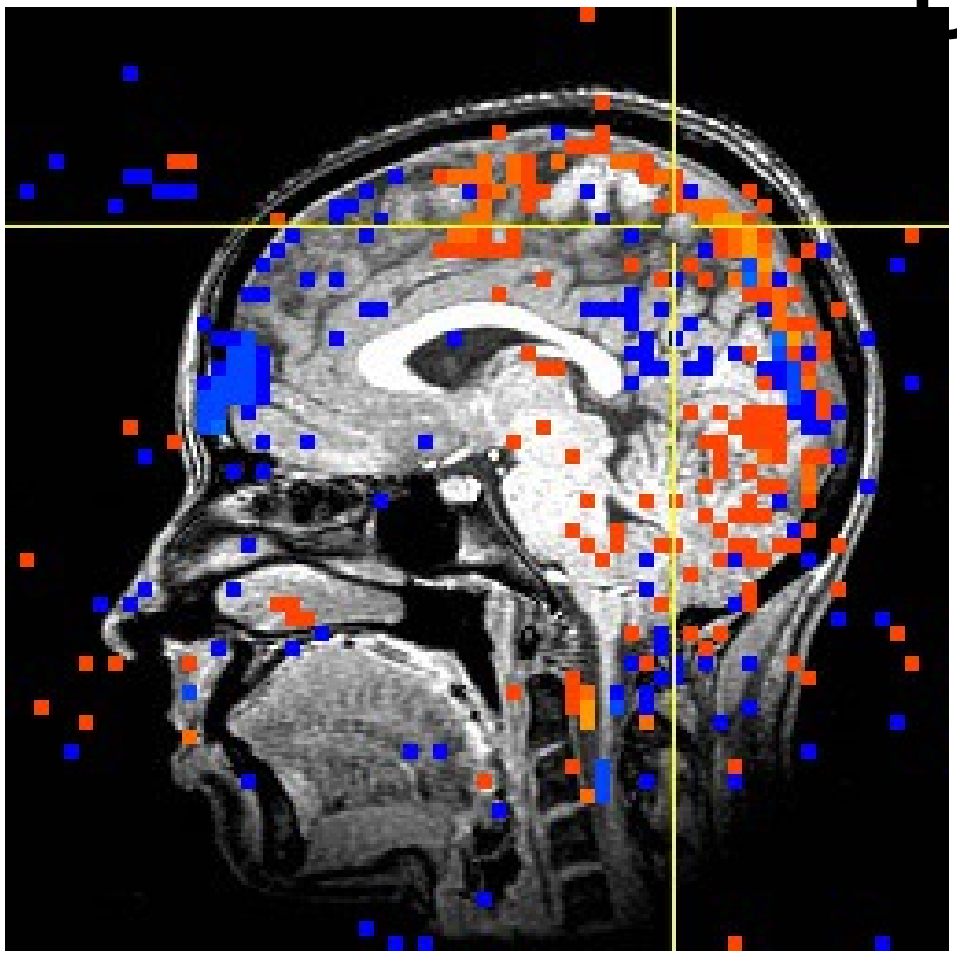
- The **BLOCK** HRF shape is useful with event-related experiment designs
- Just use a short duration, such as 1 second
- Real experiments have more than 4 task repetitions!

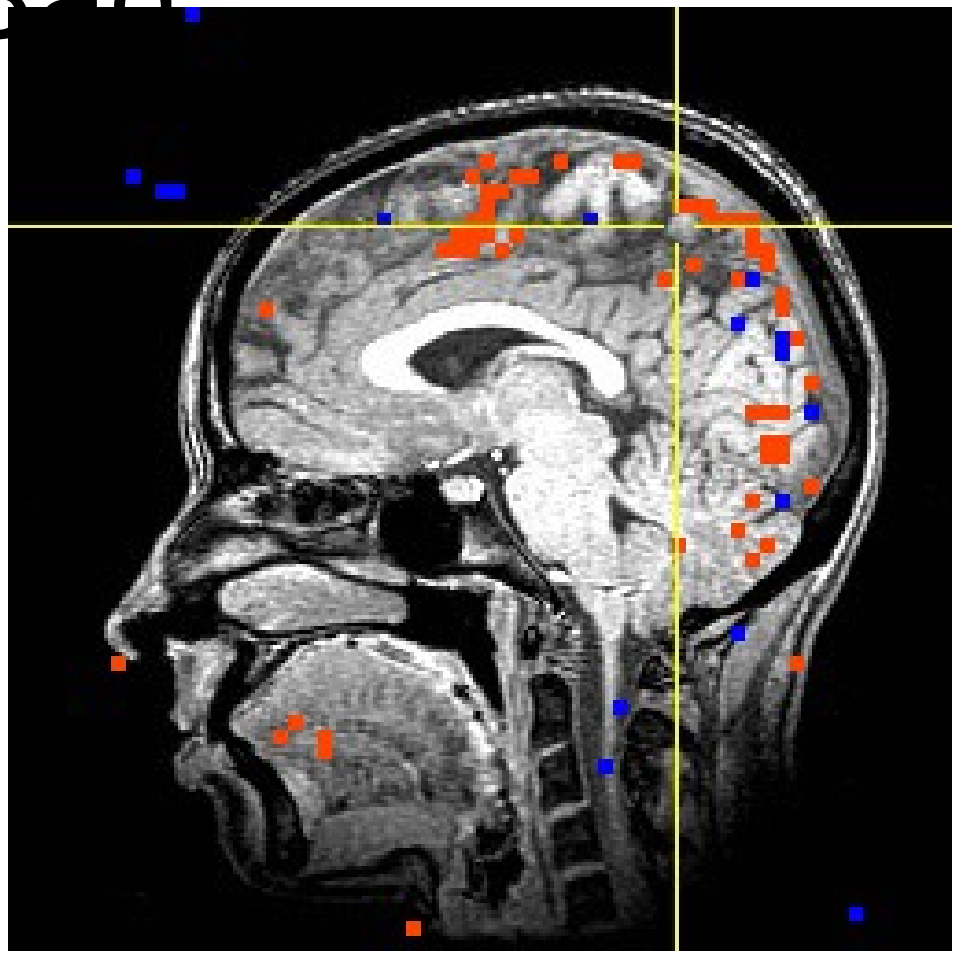


Linear Model with Fixed-Shape HRF

- FMRI data = baseline + drift + other effects of no interest + response$_1$ + … + 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]
- $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$, $\mathbf{X} = [1, t, t^2, x_1, x_2, \ldots, x_k, \ldots]$ [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





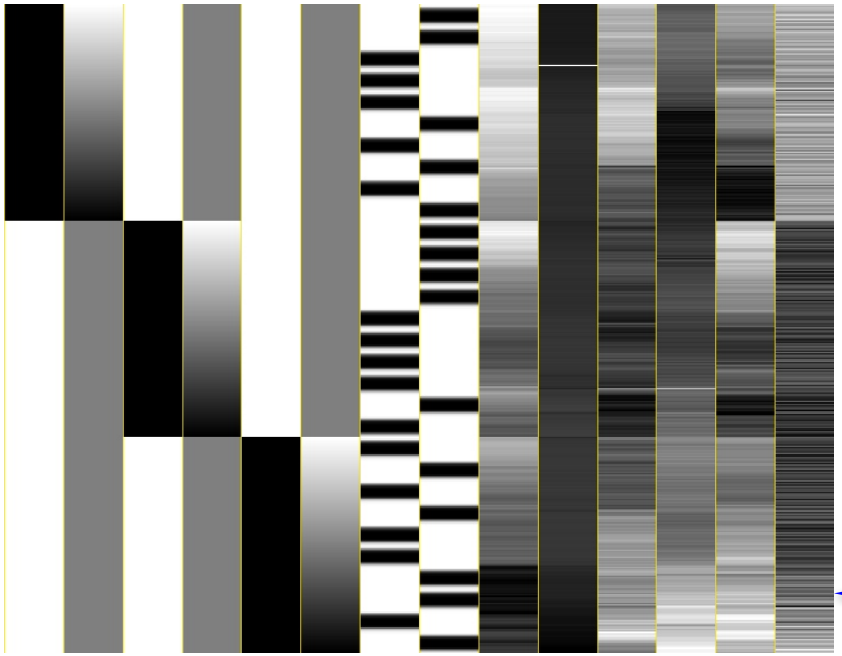
Activation map with image registration but *without* using movement estimates as regressors

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

baseline + drift stimuli head motion

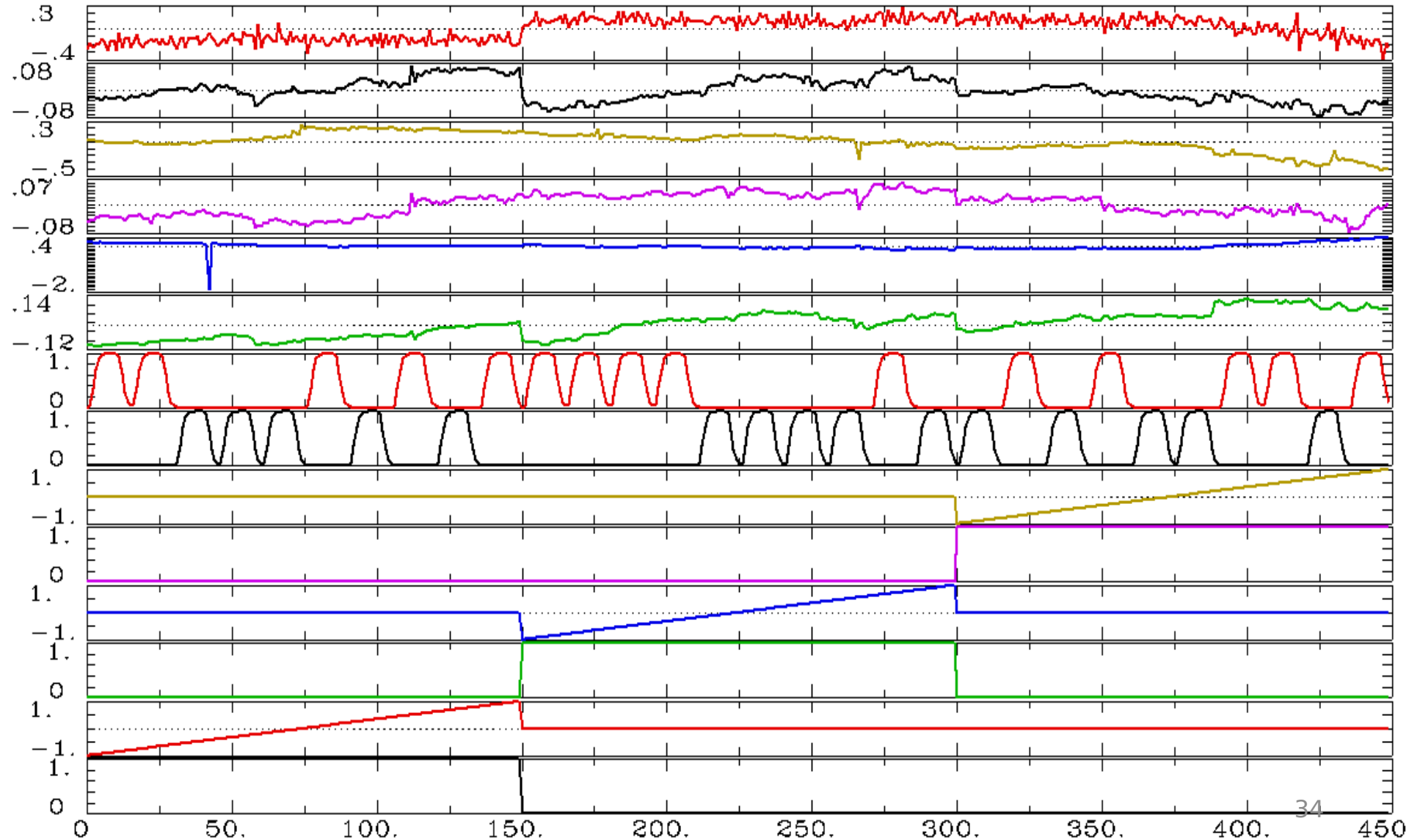


- 6 drift effect regressors
  - linear baseline
  - 3 runs x 2 parameters/run
- 2 regressors of interest
  - that is, relevant to brain activity
- 6 head motion regressors
  - 3 rotations + 3 shifts

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



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!
```

This message is usually due to setup mistakes

  - Full *F*-statistic (automatically provided in AFNI); testing
    - Data = 'baseline' + effects of interest + noise ***versus***
      Data = 'baseline' + noise
  - or, Determination coefficient R^2 at activated regions (-rout in 3dDeconvolve):
    - 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!
- Effects (regression coefficients) of interest
  - β: effect relative to baseline condition (by default in AFNI)
    - $\beta_A = \text{Effect}_A - \beta_{base}$
  - *t*-statistic: statistical significance of a β
- 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: statistical significance of this difference
- General linear test – linear combination of multiple effects
  - *t*-statistic of 0.5*happy + 0.5*sad – neutral
- Composite tests
  - *F*-statistic for composite (multi-part) null hypotheses: happy = sad = neutral = 0 [3 parts]; or, happy = sad = neutral [2 parts]

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

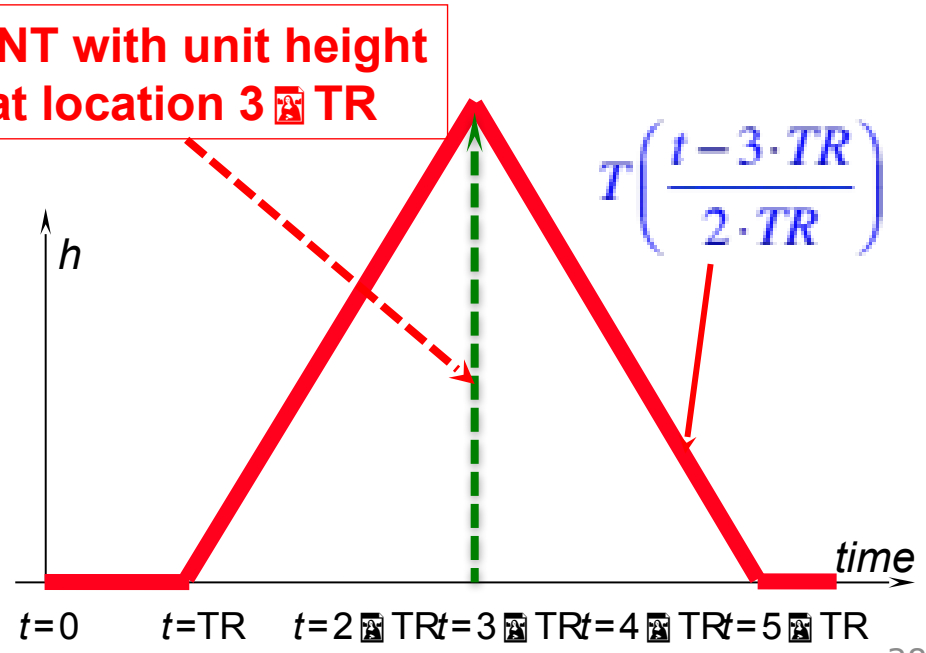
Alternative: No Constraint on HRF Shape

- TENT expansion of HRF
  - Set multiple tents at various equally-spaced locations to cover the potential BOLD response period
    - Each TENT is a **basis function**
    - 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

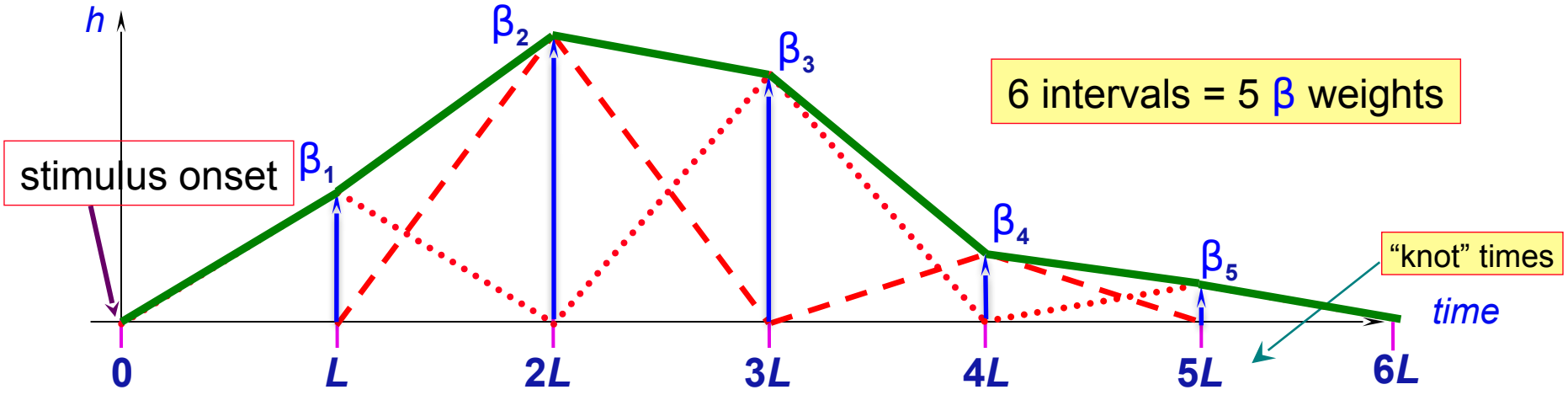
Cubic splines (CSPLIN) are also available in AFNI



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

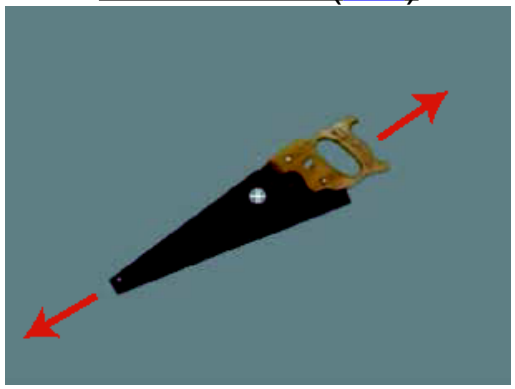
Modeling with TENTs - Example

- 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)

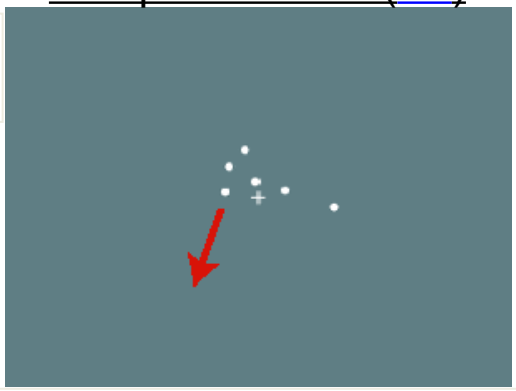
Tool motion (TM)



Human point motion (HP)

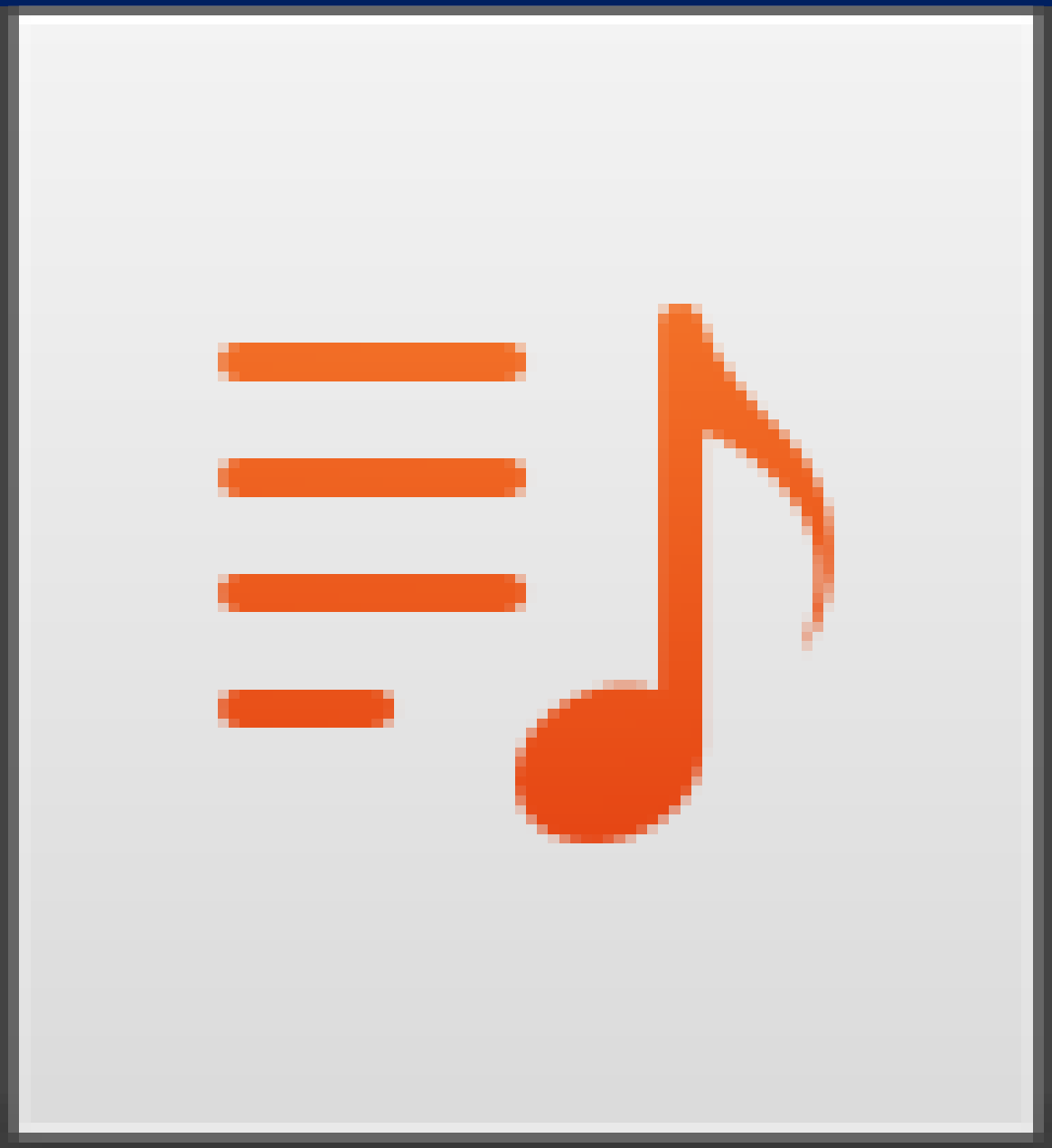
From Figure 1
Beauchamp et al. 2003

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)

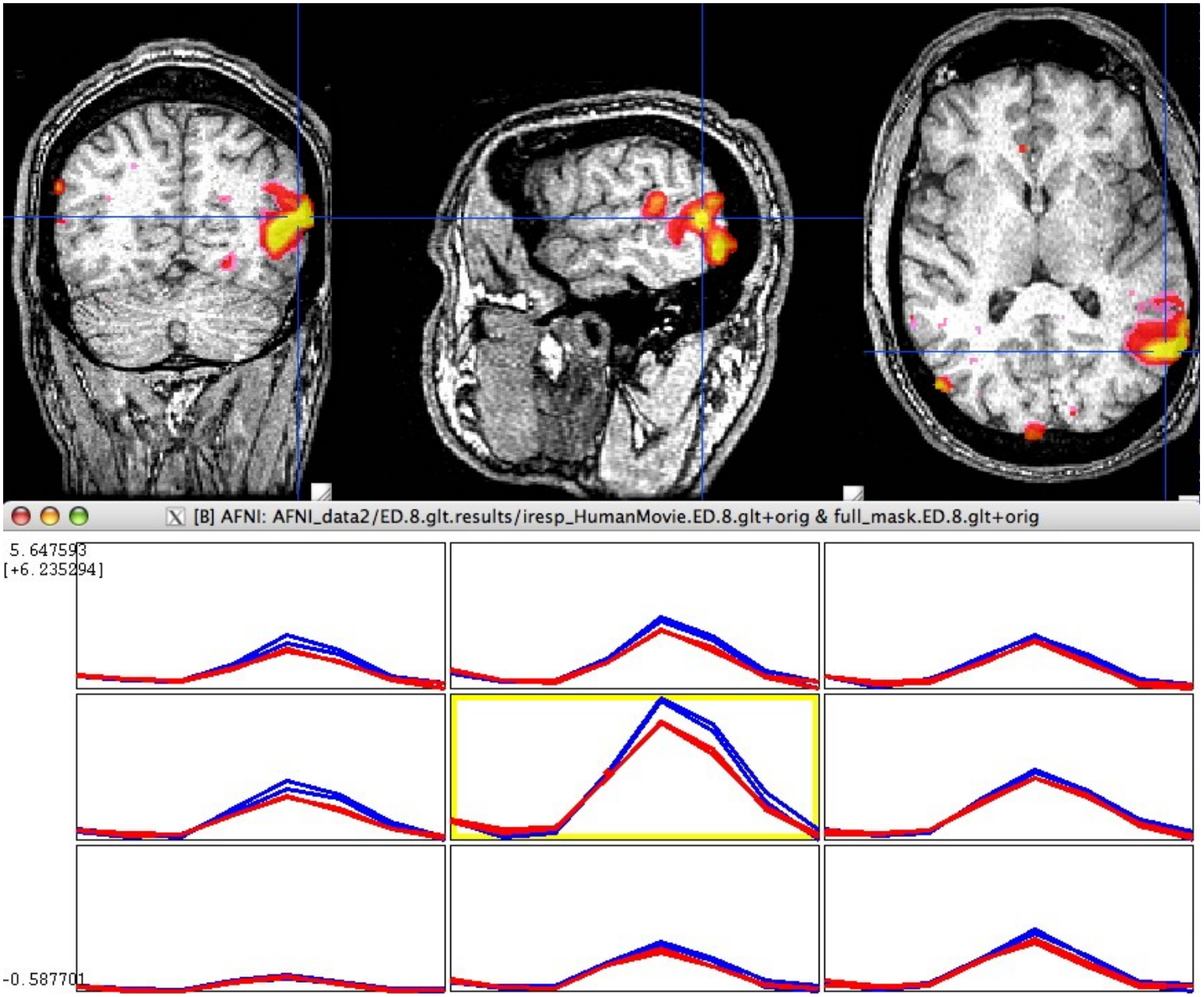
Design Matrix with `TENTzero(0,16,9)`

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
    - Like multiplication, we have to know two and estimate the 3rd
  - Fixed-shape approach: Convolution + regression
    - Known: HRF shape, stimulus
    - Use convolution to create regressors (hidden from user inside 3dDeconvolve program)
    - 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

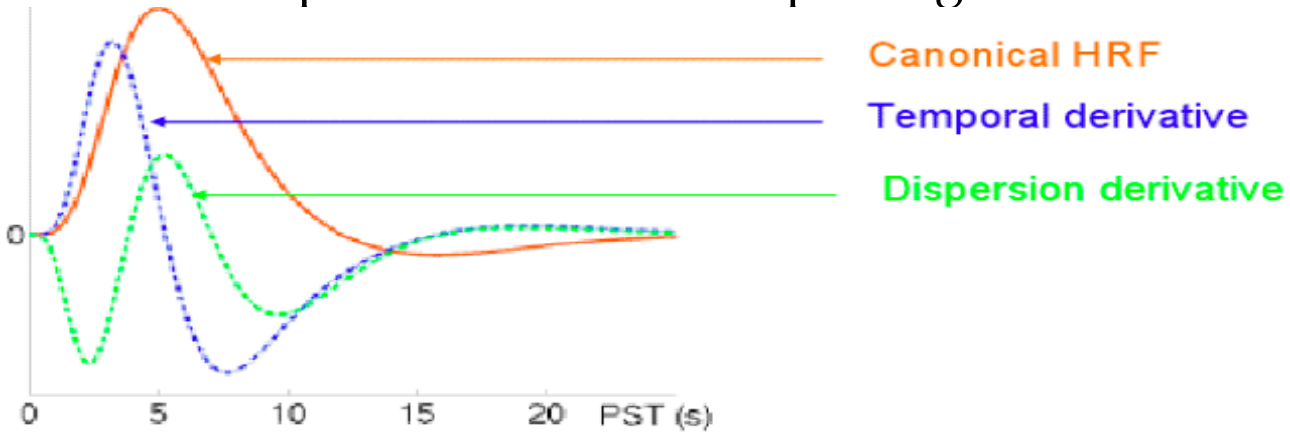
- What is the approach good at?
  - Usually for event-related experiments, but can be used for BLOCK
    - Multiple basis functions for blocks: within-block attenuation with time
  - Likely to have more accurate estimate on HDR shape across
    - subject
    - conditions/tasks
    - brain regions
  - 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

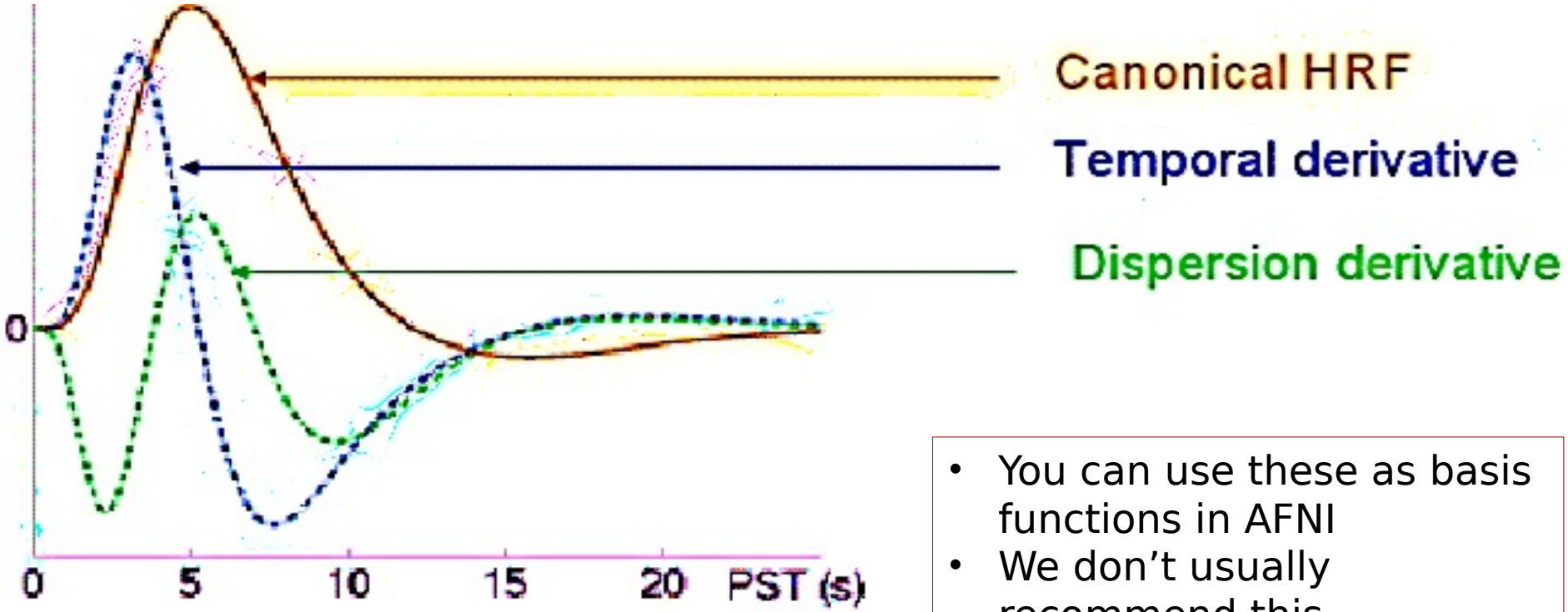
      $a_1 = 0.0083333333$ $p1 = 5$ (main positive lobe)

      $a_2 = 1.274527e\text{-}13$ $p2 = 15$ (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: $y = X\beta+\varepsilon$
  - 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 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

Percent Signal Change

- Why not use scaled βs 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 βs before group analysis
    - Simpler to 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: 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

References for further reading

- **Beta weights/effect estimates are important:**
  Chen G, Taylor PA, Cox RW (2017). Is the statistic value all we should care about in neuroimaging? Neuroimage. 147:952-959. doi:10.1016/j.neuroimage.2016.09.066
  https://pubmed.ncbi.nlm.nih.gov/27729277/
- **AFNI's 3dREMLfit has quite good performance for autocorrelation modeling:**
  Olszowy W, Aston J, Rua C, Williams GB (2019). Accurate autocorrelation modeling substantially improves fMRI reliability. Nature Communications 10, 1220. doi.org/10.1038/s41467-019-09230-w
  https://www.nature.com/articles/s41467-019-09230-w
- **Modeling a detailed HRF is likely very important:**
  Chen G, Taylor PA, Reynolds RC, Leibenluft E, Pine DS, Brotmas MA, Pagliaccio D, Haller SP (2023). BOLD response is more than just magnitude: improving detection sensitivity through capturing hemodynamic profiles. Neuroimage 277:120224.
  https://pubmed.ncbi.nlm.nih.gov/37327955/