Statistics of FMRI

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Scientific and Statistical Computing Core

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Overview of FMRI Statistics

- What is statistics? What is statistical testing?
- Experiment design
  - How to efficiently squeeze the signal of interest into the data
- Typical statistical models involved in FMRI
  - Regression: individual level
  - General linear model (GLM): group level
    - Student's t-tests: one-, two-sample, or paired
    - Multiple regression
    - AN(C)OVA
  - Linear mixed-effects (LME) model
- Miscellaneous

What is statistics?

- In God we trust. All others must bring **data**!
  - Related to *state* and *status*: science of state
  - German *statistik* by Gottfried Achenwall (1749)
- Statistics is about dealing with variation (noise)
  - Noise is annoying, but contains a lot of useful information
  - Art of noise handling
- Science of data analysis based on variation
  - Data collection
  - Model building, comparison, selection and analysis
  - Inference and interpretation
  - Presentation and prediction

Is our brain statistically wired?

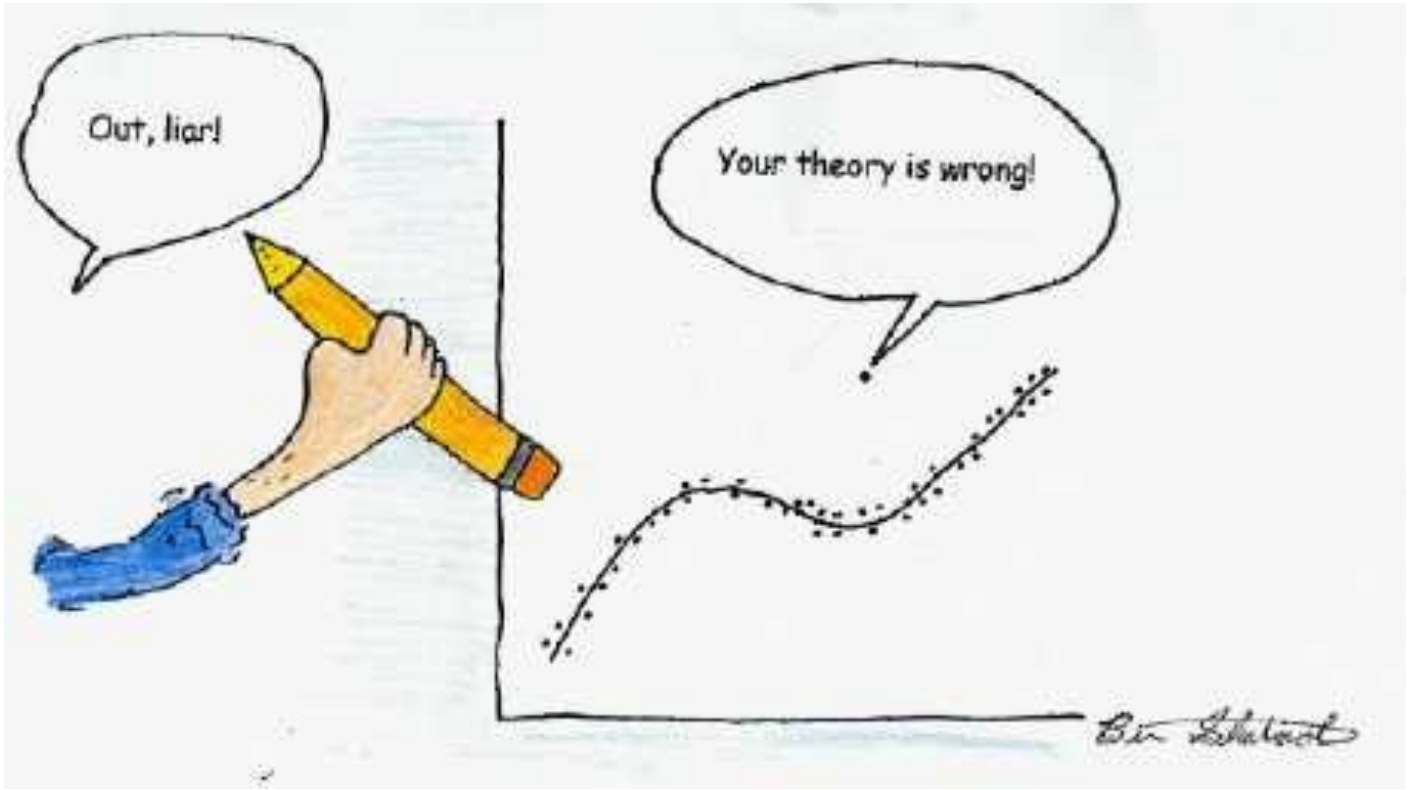
- Example 1
  - Should we buy lottery tickets and insurances?
- Example 2
  - Average deaths due to snakebites in the USA and Canada per year? *15*
  - Average deaths in air transport per year in the USA? *200*
  - Average number of people killed by cars annually in the USA? *40,000*
- Example 3
  - Suppose I flip a coin 5 times, and get all heads. What is the chance of getting a head in the next toss?
- Example 4
  - HIV prevalence = 0.1%, false + of HIV test = 5%, power of HIV test ~ 100%. P(HIV+ | test+) = ?

$$P(HIV+ \mid test+) = \frac{P(test+, HIV+)}{P(test+)} = \frac{P(test+ \mid HIV+)P(HIV+)}{P(test+ \mid HIV+)P(HIV+) + P(test+ \mid HIV-)P(HIV-)} = \frac{1.0 \times 10^{-3}}{1.0 \times 10^{-3} + 0.05 \times (1 - 10^{-3})} \approx 0.02$$

Statistics in daily life

- Census in Bible
- Stereotype: economical thinking
- Miss a step when walking downstairs
- Lottery and gambling
  - Dream of a huge gain out of an unlikely occurrence by paying > expected value
- Insurance
  - Risk management: hedge the risk of contingency losses
  - Opposite of lottery: Avoid a huge incidental loss by paying > expected cost
  - Airbags, ABS, alarm systems, security monitoring system…
- Surveys, clinical trials, …

Statistics: massaging data?



Statistics: or massaging statisticians?

Experiment Designs

- FMRI experiment types
  - Task-based
    - Block design
    - Event-related
    - Mixed type
  - Resting state
    - Relaxing with eyes closed
  - Naturalistic FMRI
    - Movie watching, music/speech listening

Experiment Design: task-based

- **Principle:** ***Jam all possible information into the design before data acquisition***
- Factors for an efficient design at the individual level
  - Number of time points (TRs)
    - Important for individual analysis, but may affect group level implicitly
    - Power: proportional to $\sqrt{DF}$
    - Limited by subject's tolerance in scanner: 30-90 min per session
  - TR length: mostly 2 sec
    - Shorter TR yields more time points (and potentially more power), but
    - Power improvement limited by weaker MR signal
    - Shorter TR → shorter ISI → higher event freq → higher correlation → less power
    - Usually limited by hardware considerations

Experiment Design: individual level

- Factors for an efficient design at the individual level
  - Complexity of the experiment: number of conditions/tasks (regressors)
    - Limited by scanning time and confounded by low frequencies
  - Sample size: number of trials per condition/task
    - The more the better, but no magic number: block or event-related?
  - Event arrangement
    - How to design? How to define the "best" design?
    - Efficiency: achieve highest statistical power within fixed scanning time
    - Randomizing trials: sequence and inter-stimulus interval (ISI)

Experiment Design: individual level

- Factors for an efficient design at the individual level
  - HDR modeling
    - Fixed-Shape Method (FSM): assuming an empirical response curve; economical but high risk of inaccuracy
    - Adjusted-Shape Method (ASM): more wiggle room for shape variability; focus on the major shape
    - Estimated-Shape Method (ESM): capable of achieve accurate shape characterization and power; challenging on group analysis

Experiment Design: group level

- Factors for an efficient design at the group level
  - Number of subjects (n)
    - Important for group analysis: inter-subject vs. intra-subject variation
    - Power (success to detect signal if present) roughly proportional to $\sqrt{n}$
    - Design type: block vs. event-related
    - Recommended: 20+
  - Design of the study
    - Complexity: factors, levels, covariates, contrasts of interest, …
    - With multiple groups, counterbalance, if possible, potential confounding effects such as age, gender, IQ, education background, socioeconomic status, etc.
- At the end of the day
  - Group level matters the most!

Modeling

- Data visualization
  - Any excessive head motion? Spikes? Abnormalities?
- Modeling building/selection
  - Individual level: time series regression
    - Regressors of interest
    - Regressors of no interest
    - Noise
  - Group level
    - *t*-tests, Regression, ANOVA, ANCOVA, GLM, LME, …
    - Nonparametric methods
      - Ranking methods
      - Permutations
      - Bootstrapping

Overview: Individual subject analysis

- Basics of linear regression model
- FMRI task-based experiment types
  - Block design; Event-related experiment; Mixed
- FMRI data decomposition: three components
  - Effects of no interest: baseline, slow drift, others; Effects of interest; *Noise*
  - Effects of interest - understanding BOLD vs. stimulus: IRF
- 3 modeling strategies
  - Model-based: presumed or fixed-shape IRF (FSM)
  - Data-driven: no assumption about IRF shape (ESM)
  - Intermediate: one major IRF plus shape adjustment (ASM)

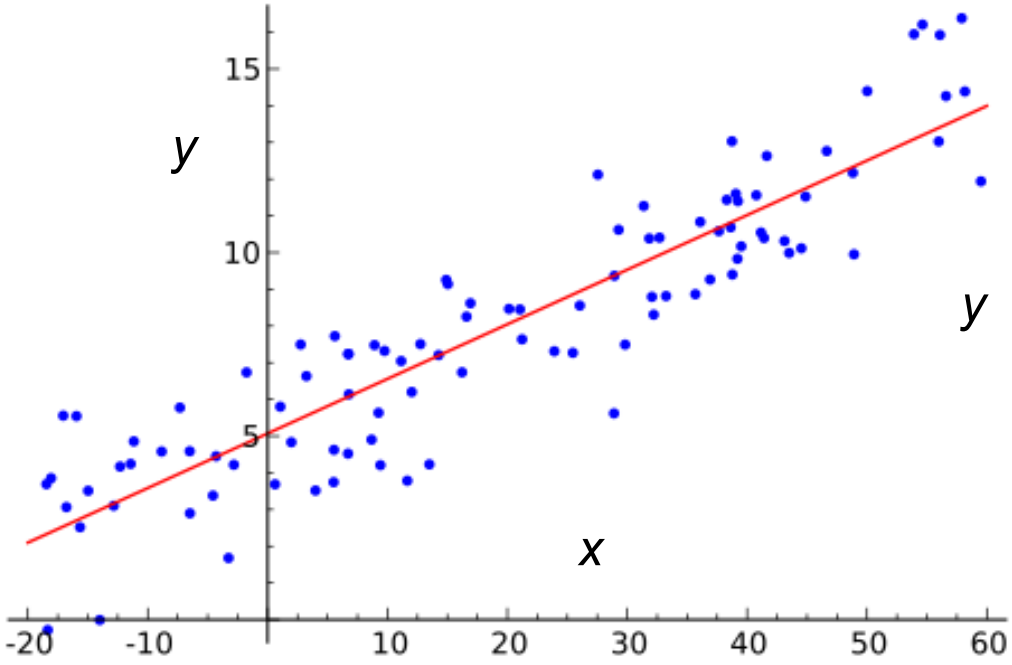
Basics of Regression

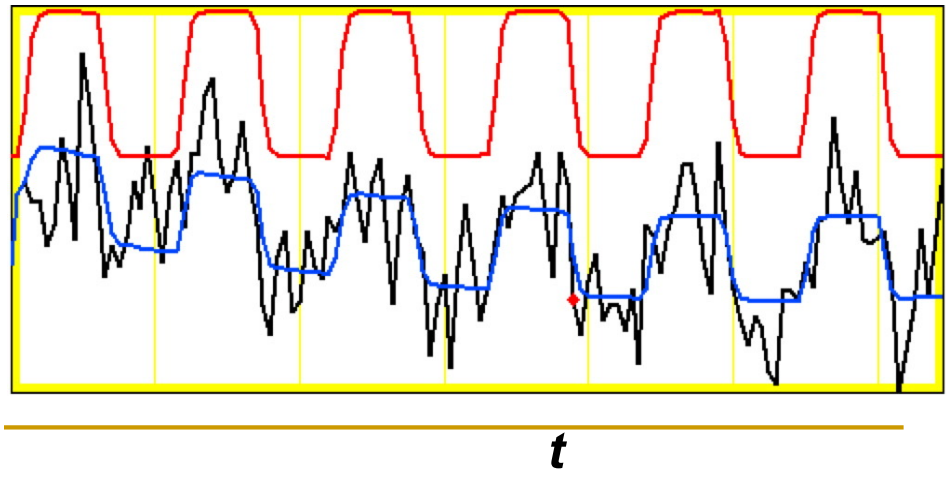
- Statistical modeling (information extraction)
  - Two goals
    - Prediction: machine learning – support vector machine (SVM)
    - Inferences: activation detection
- Regression: relationship between a response/outcome (dependent) variable and one or more explanatory (independent) variables (regressors)
  - 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
    - Psychology (Daniel Kahneman): Rewards for good performance vs. punishment of mistakes (correlation vs. causation)
    - Lost in most cases including FMRI
  - Some statisticians call it (general) linear model

Basics of Regression

- Mathematical formulation
  - $y_i = \alpha + \beta_1 x_{1i} + \ldots + \beta_k x_{ki} + \varepsilon_i$, i: time index
  - $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$, $\mathbf{X} = [1, x_1, x_2, \ldots, x_k]$
  - Assumptions
    - linearity
    - white noise (independence) and

      Gaussianity $\boldsymbol{\varepsilon} \sim N(0, \sigma^2\mathbf{I})$





Basics of Regression

- Solution for regression $\boldsymbol{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$
  - Project data **y** onto the space of explanatory variables (**X**)
  - OLS $\hat{\beta} = (X^T X)^{-1} X^T y$
- Interpreting β values: slope, marginal effect, or effect estimate associated with a regressor (explanatory variable)
- Various statistical tests
  - *t*-test for each β (H_0: $\beta_{sad} = 0$)
  - *t*-test for linear combination of β values - general linear test (GLT), *e.g.*, H_0: $\beta_{hap} - \beta_{sad} = 0$, or H_0: $0.5*(\beta_{hap}+\beta_{sad}) - \beta_{neu} = 0$
  - *F*-test for composite null hypothesis, *e.g.*, H_0: $\beta_{hap} = \beta_{sad} = \beta_{neu}$ or H_0: $\beta_{hap} = \beta_{sad} = \beta_{neu} = 0$
  - Omnibus or overall *F*-test for the **whole** model, *e.g*, H_0: all β's = 0, or for a **partial** model H_0: all β's of interest = 0

Regression with FMRI

- Time series regression: data $\boldsymbol{y}$ is time series
  - Regressors: idealized responses or basis functions
  - Special handling: noise not white $\boldsymbol{\varepsilon} \sim N(0, \sigma^2\boldsymbol{\Sigma})$, but 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
  - $\boldsymbol{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$: same design matrix **X** across the brain

FMRI Data

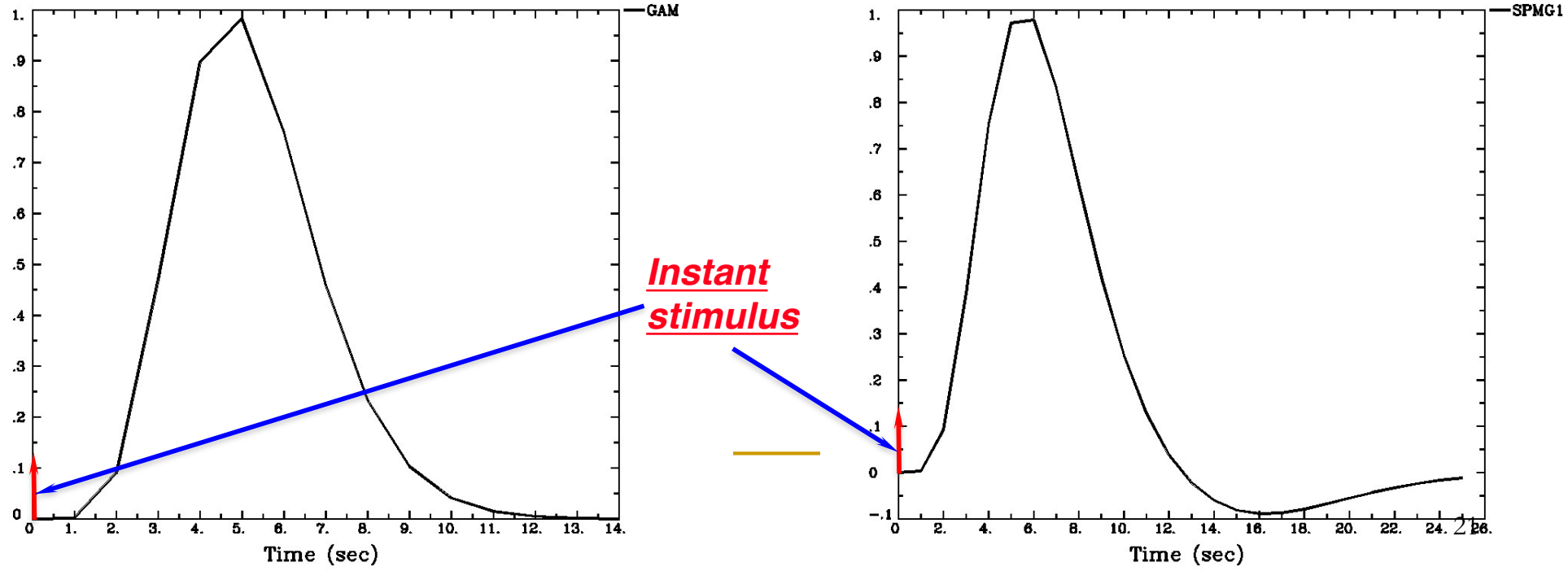
- Data partition: **Data = Signal + Noise**
  - **Data** = acquisition from scanner (voxel-wise time series)
  - **Signal** = BOLD response to stimulus; effects of interest + no interest
    - We don't fully know the real signal!
    - Look for idealized components, or search for signal via repeated trials
    - Of interest: effect estimate (response amplitude) for each condition
    - 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, or 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 handle the effects of no interest?
  - How to construct the regressors of interest (responses)?
  - Assumptions about the noise?

Effects of interest

- data = effects of no interest+response$_1$+…+response$_k$ + noise
- 3 components: baseline + drift + other effects of no interest
  - Baseline (and drift) can be modeled as an additive effect (AFNI), or an effect of interest (*cf.* SPM and FSL)
  - Drift: psychological/physiological effect + thermal fluctuation; modeled with polynomials
  - $y_i = \alpha_0 + \alpha_1 t_i + \alpha_1 t_i^2 + \beta_1 x_{1i} + \ldots + \beta_k x_{ki} + \ldots + \varepsilon_i$
  - $\boldsymbol{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}, \mathbf{X} = [1, t, t^2, x_1, x_2, \ldots, x_k, \ldots]$
  - Other effects of no interest: head motion effects, censored time points, …

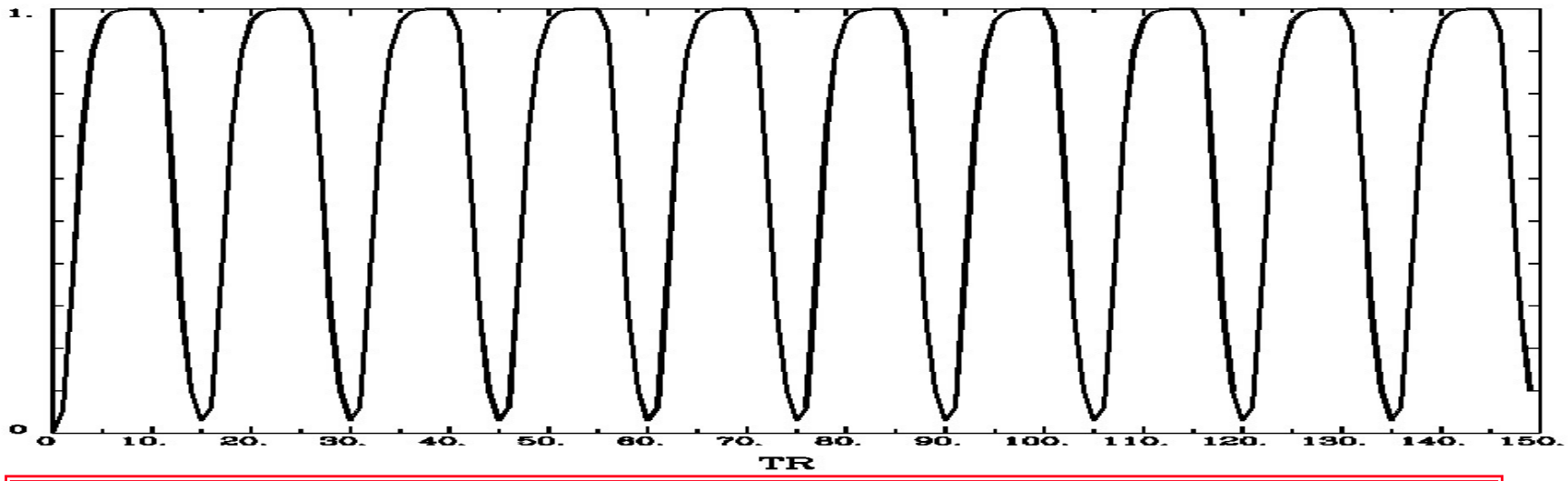
Constructing Regressors: FSM

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



FSM for Block Design

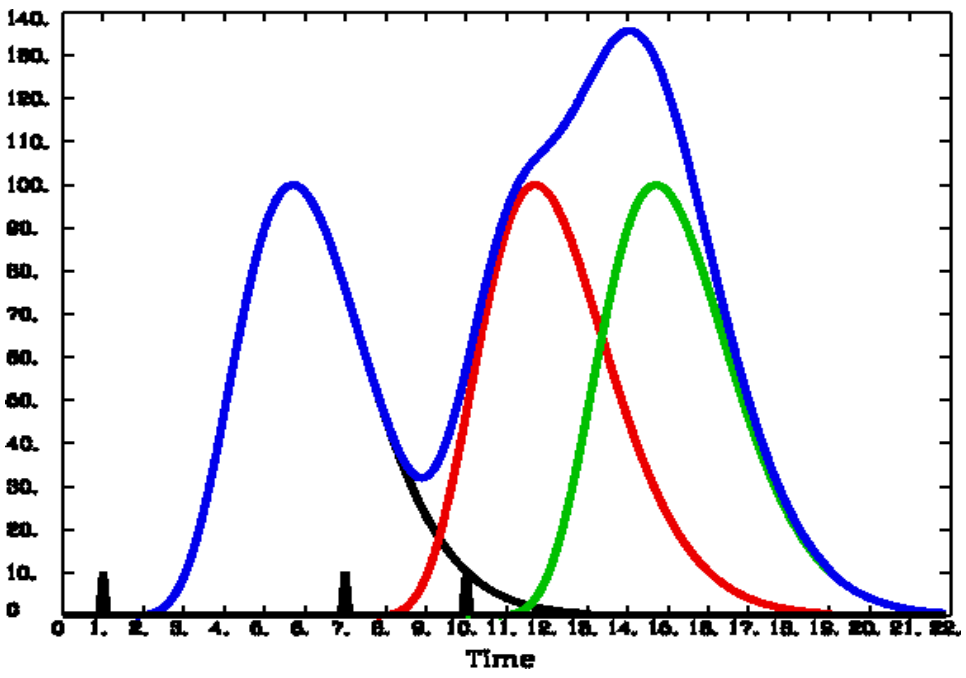
- Presuming a fixed shape IRF $h(t)$ for each instantaneous stimulus – 3 parameters: onset, duration, peak
  - For each block, $h(t)$ is convolved with stimulus timing and duration (d) to get idealized response (temporal pattern) as an explanatory variable (regressor): BLOCK(d,p)
    - Equivalent to convolving a series of consecutive events
    - Linearity assumed within each block: plateau-like response
    - p: scale HDF to 1 for easy interpretation of β

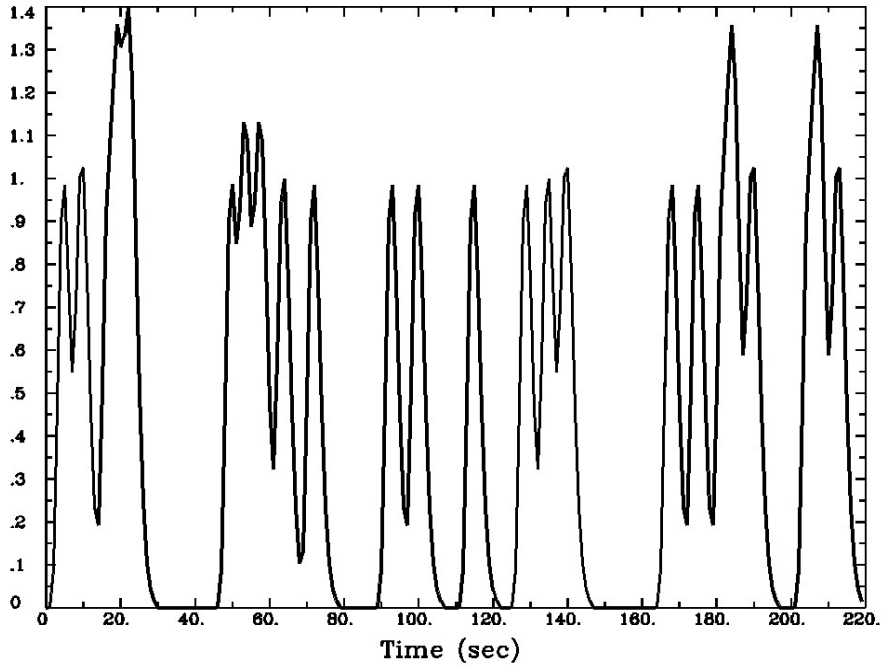


Block: 10 s on and 10 s off; TR=2 s; 150 time points

FSM for Event-Related Design

- Fixed shape IRF $h(t)$ for an instantaneous stimulus – 2 parameters: timing and peak
  - For multiple trials 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) or BLOCK(0)





Assessing FSM

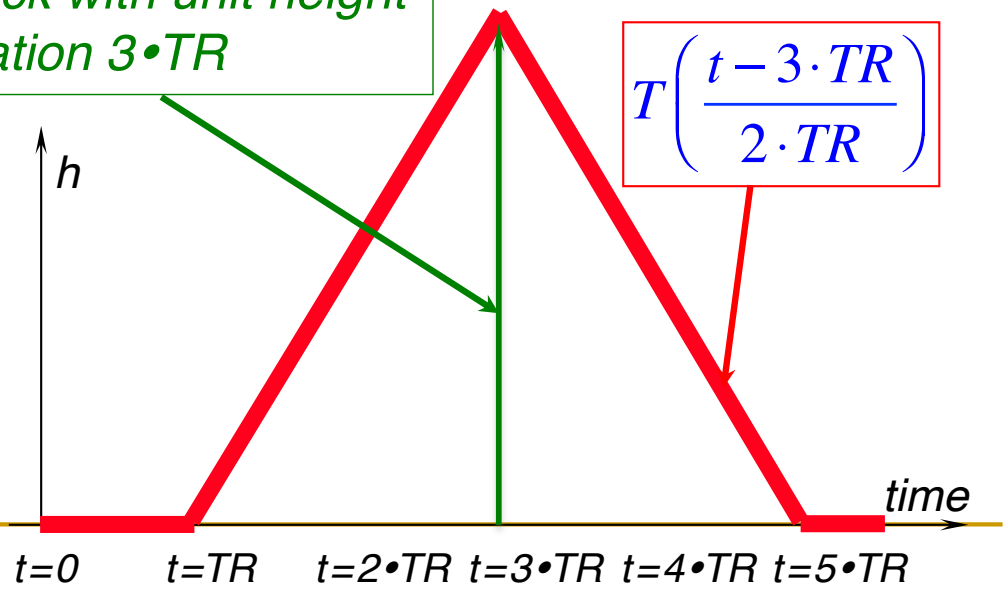
- Used 99% of time, but not necessarily the optimal
  - Assumes brain responds with **same shape** across 4 levels: subjects, activated regions, stimulus conditions/tasks, trials
    - Difference in magnitude β and its significance
    - Strong assumption about 4 levels regarding shape
  - Easy to handle: 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
      - Linearity when two responses overlap? Same effect across events?
- Not desirable if you
  - Care about subtle shape difference across subjects, across regions, across conditions, and across trials
  - Improve model fitting

ESM: 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
    - Each yardstick or TENT is a basis function
  - BOLD response measured by yardstick heights at all locations
    - 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

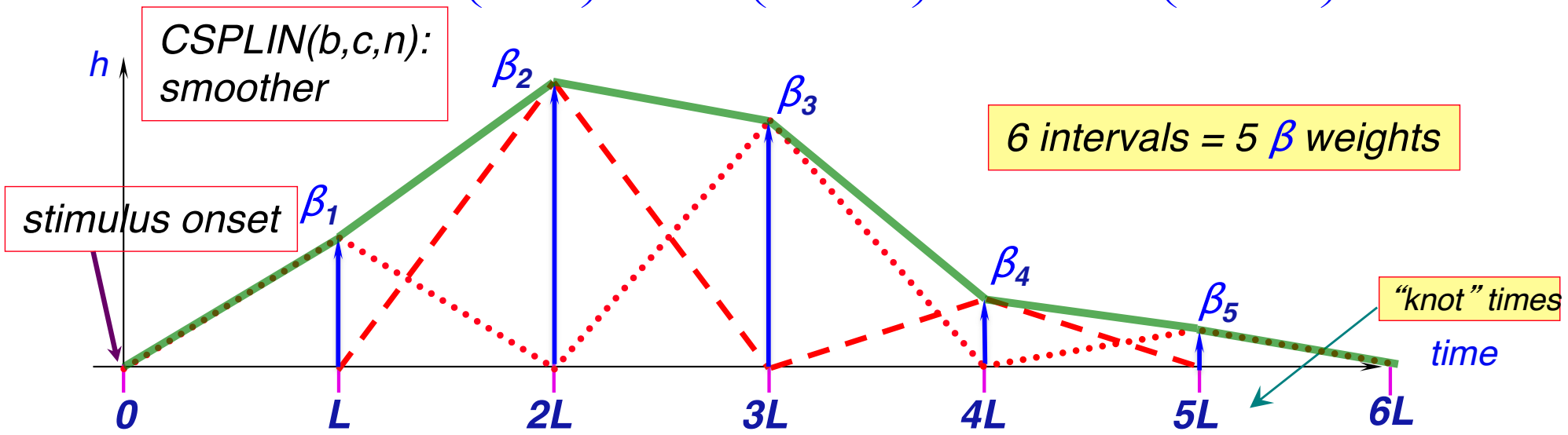


Cubic splines are also available

Tent Functions = Linear Interpolation

- 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 ($L \geq$ TR), *e.g.*, with TR=2s, L=2, 4s

Assessing ESM

- Pros
  - Usually for event-related experiments, but can be used for BLOCK
    - Multiple basis functions for blocks: within-block attenuation/habituation
    - Cross-block attenuation/habituation?
  - Likely to have more accurate estimate on HDR shape across subjects, conditions/tasks, brain regions
  - Likely to have better model fit
  - Likely to be statistically more powerful
- Cons
  - Difficult to summarize at group level: group analysis capability
  - A few times more regressors than alternatives: DF's
  - Risk of highly correlated regressors: multicollinearity
    - Try changing the number of basis functions
  - Over-fitting: picking up something (head motion) unrelated to HDR

Why Group Analysis?

- Reproducibility and generalization
  - Science strives for generality: summarizing subject results
  - Typically 10 or more subjects per group
  - Exceptions: pre-surgical planning, lie detection, …
- Why not one analysis with a mega model for all subjects?
  - Computationally unmanageable
  - Heterogeneity in data or experiment design across subjects
  - Model quality check at individual subject level

Toy example of group analysis: FSM

- Responses from a group of subjects under one condition
  - What we have: (β_1, β_2, …, β_{10})=(1.13, 0.87, …, 0.72)
- Centroid: average $(\beta_1+\beta_2+\ldots+\beta_{10})/10 = 0.92$ is not enough
  - Variation/reliability measure: diversity, spread, deviation
- Model building
  - Subject *i*'s response = group average + deviation of subject *i*: simple model GLM (one-sample *t*-test)

$$\hat{\beta}_i = b + \epsilon_i, \epsilon_i \sim N(0, \sigma^2)$$

  - If individual responses are consistent, ϵ_i should be small
    - *t*-test: significance measure = $\frac{\hat{b}}{\hat{\sigma}/n}$
    - 2 measures: *b* (dimensional) and *t* (dimensionless)

Models at Group Level: FSM

- Conventional approach: taking β (or linear combination of multiple β's) only for group analysis
  - Assumption: all subjects have same precision (reliability, standard error, confidence interval) about
  - All subjects are treated equally
  - Student's *t*-test: paired, one- and two-sample: not random-effects models in strict sense as usually claimed
  - AN(C)OVA, GLM, LME
- Alternative: taking both effect estimates and *t*-statistics
  - *t*-statistic contains precision information about effect estimates
  - Each subject is weighted based on precision of effect estimate

Classical ANOVA: 2 × 3 Mixed ANCOVA

- Factor A (Group): 2 levels (patient and control)
- Factor B (Condition): 3 levels (pos, neg, neu)
- Factor S (Subject): 15 ASD children and 15 healthy controls
- Covariate (Age): **cannot** be modeled; **no** correction for sphericity violation

$$F_{(a-1,a(n-1))}(A) = \frac{MSA}{MSS(A)},$$
$$F_{(b-1,a(b-1)(n-1))}(B) = \frac{MSB}{MSE},$$
$$F_{((a-1)(b-1),a(b-1)(n-1))}(AB) = \frac{MSAB}{MSE},$$

where

$$MSA = \frac{SSA}{a-1} = \frac{1}{a-1}\left(\frac{1}{bn}\sum_{j=1}^{a} Y_{.j.}^2 - \frac{1}{abn}Y_{...}^2\right),$$
$$MSB = \frac{SSB}{b-1} = \frac{1}{b-1}\left(\frac{1}{an}\sum_{k=1}^{b} Y_{..k}^2 - \frac{1}{abn}Y_{...}^2\right),$$
$$MSAB = \frac{SSAB}{(a-1)(b-1)} = \frac{1}{(a-1)(b-1)}\left(\frac{1}{n}\sum_{j=1}^{a}\sum_{k=1}^{b} Y_{.jk} - \frac{1}{bn}\sum_{j=1}^{a} Y_{.j.}^2 - \frac{1}{an}\sum_{k=1}^{b} Y_{..k}^2 + \frac{1}{abn}Y_{...}^2\right),$$
$$MSS(A) = \frac{SSS(A)}{a(n-1)} = \frac{1}{a(n-1)}\left(\frac{1}{b}\sum_{i=1}^{n}\sum_{j=1}^{a} Y_{ij.}^2 - \frac{1}{bn}\sum_{j=1}^{a} Y_{.j.}^2\right),$$
$$MSE = \frac{1}{a(b-1)(n-1)}\left(\sum_{i=1}^{n}\sum_{j=1}^{a}\sum_{k=1}^{b} Y_{ijk}^2 - \frac{1}{n}\sum_{j=1}^{a}\sum_{k=1}^{b} Y_{.jk} - \frac{1}{b}\sum_{i=1}^{n}\sum_{j=1}^{a} Y_{ij.}^2 + \frac{1}{bn}\sum_{j=1}^{a} Y_{.j.}^2 + \frac{1}{abn}Y_{...}^2\right)$$

Univariate GLM: 2 x 3 mixed ANOVA

- Group: 2 levels (patient and control)
- Condition: 3 levels (pos, neg, neu)
- Subject: 3 ASD children and 3 healthy controls

Difficult to incorporate covariates
- *Broken orthogonality*

No correction for sphericity violation

$$
\begin{array}{c}\text{Subj}\\ 1\\1\\1\\2\\2\\2\\3\\3\\3\\4\\4\\4\\5\\5\\5\\6\\6\\6\end{array}
\begin{pmatrix}\beta_{11}\\\beta_{12}\\\beta_{13}\\\beta_{21}\\\beta_{22}\\\beta_{23}\\\beta_{31}\\\beta_{32}\\\beta_{33}\\\beta_{41}\\\beta_{42}\\\beta_{43}\\\beta_{51}\\\beta_{52}\\\beta_{53}\\\beta_{61}\\\beta_{62}\\\beta_{63}\end{pmatrix}
= b
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1&1&1&0&1&0&1&0&0&0\\1&1&0&1&0&1&1&0&0&0\\1&1&-1&-1&-1&-1&1&0&0&0\\
1&1&1&0&1&0&0&1&0&0\\1&1&0&1&0&1&0&1&0&0\\1&1&-1&-1&-1&-1&0&1&0&0\\
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X
\begin{pmatrix}\alpha_0\\\alpha_1\\\alpha_2\\\alpha_3\\\alpha_4\\\alpha_5\\\alpha_6\\\alpha_7\\\alpha_8\\\alpha_9\end{pmatrix}
a
+
\begin{pmatrix}\delta_{11}\\\delta_{12}\\\delta_{13}\\\delta_{21}\\\delta_{22}\\\delta_{23}\\\delta_{31}\\\delta_{32}\\\delta_{33}\\\delta_{41}\\\delta_{42}\\\delta_{43}\\\delta_{51}\\\delta_{52}\\\delta_{53}\\\delta_{61}\\\delta_{62}\\\delta_{63}\end{pmatrix}
d
$$

Flexible Approach: Multivariate GLM

- Group: 2 levels (patient and control)
- Condition: 3 levels (pos, neg, neu)
- Subject: 3 ASD children and 3 healthy controls
- Age: quantitative covariate

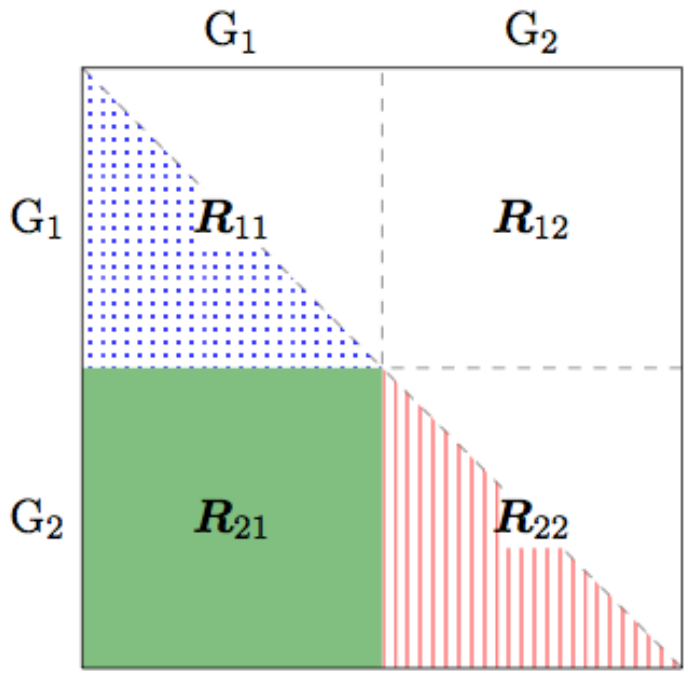
$$\boldsymbol{B}_{n\times m} = \boldsymbol{X}_{n\times q}\,\boldsymbol{A}_{q\times m} + \boldsymbol{D}_{n\times m}$$

$$\begin{array}{c} Subj \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array}\begin{array}{c} \begin{pmatrix} Pos & Neg & Neu \\ \beta_{11} & \beta_{12} & \beta_{13} \\ \beta_{21} & \beta_{22} & \beta_{23} \\ \beta_{31} & \beta_{32} & \beta_{33} \\ \beta_{41} & \beta_{42} & \beta_{43} \\ \beta_{51} & \beta_{52} & \beta_{53} \\ \beta_{61} & \beta_{62} & \beta_{63} \end{pmatrix} \\ B \end{array} = \begin{array}{c} \begin{pmatrix} Int & Grp & Age \\ 1 & 1 & -6 \\ 1 & 1 & 10 \\ 1 & 1 & 4 \\ 1 & -1 & -4 \\ 1 & -1 & -1 \\ 1 & -1 & -3 \end{pmatrix} \\ X \end{array} \begin{array}{c} \begin{pmatrix} Pos & Neg & Neu \\ \alpha_{01} & \alpha_{02} & \alpha_{03} \\ \alpha_{11} & \alpha_{12} & \alpha_{13} \\ \alpha_{21} & \alpha_{22} & \alpha_{23} \end{pmatrix} \\ A \end{array} + \begin{array}{c} \begin{pmatrix} Pos & Neg & Neu \\ \delta_{11} & \delta_{12} & \delta_{13} \\ \delta_{21} & \delta_{22} & \delta_{23} \\ \delta_{31} & \delta_{32} & \delta_{33} \\ \delta_{41} & \delta_{42} & \delta_{43} \\ \delta_{51} & \delta_{52} & \delta_{53} \\ \delta_{61} & \delta_{62} & \delta_{63} \end{pmatrix} \\ D \end{array} \begin{array}{c} Subj \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array}$$

Inter-Subject Correlation (ISC)

- Analysis methodology
  - Regression with task-related regressors won't work
  - Voxel-wise correlation between any subject pair
    - n = 4 subjects => 6 ISC; n = 5 subjects → 10 ISC
    - n subjects => $n(n\text{-}1)/2$ ISC – which are not all independent!
  - How to go about group analysis?

$$
\begin{array}{c} \\ S_1 \\ S_2 \\ S_3 \\ \vdots \\ S_n \end{array}
\begin{array}{c}
\begin{array}{cccccc} S_1 & S_2 & S_3 & \cdots & S_n \end{array} \\
\begin{pmatrix}
- & z_{12} & z_{13} & \cdots & z_{1n} \\
z_{21} & - & z_{23} & \cdots & z_{2n} \\
z_{31} & z_{32} & - & \cdots & z_{3n} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
z_{n1} & z_{n2} & z_{n3} & \cdots & -
\end{pmatrix}
\end{array}
$$



Inter-Subject Correlation (ISC)

- Analysis methodology
  - How to go about group analysis?
    - Difficulty: The ISCs are not independent with each other
    - The correlations are correlated themselves!
  - Solutions
    - Permutations
    - Bootstrapping
    - LME

$$
\begin{array}{c} \\ Z_{21} \\ Z_{31} \\ Z_{41} \\ Z_{51} \\ Z_{32} \\ Z_{42} \\ Z_{52} \\ Z_{43} \\ Z_{53} \\ Z_{54} \end{array}
\begin{array}{c}
\begin{array}{cccccccccc} Z_{21} & Z_{31} & Z_{41} & Z_{51} & Z_{32} & Z_{42} & Z_{52} & Z_{43} & Z_{53} & Z_{54} \end{array} \\
\begin{pmatrix}
1 & \rho & \rho & \rho & \rho & \rho & \rho & 0 & 0 & 0 \\
\rho & 1 & \rho & \rho & \rho & 0 & 0 & \rho & \rho & 0 \\
\rho & \rho & 1 & \rho & 0 & \rho & 0 & \rho & 0 & \rho \\
\rho & \rho & \rho & 1 & 0 & 0 & \rho & 0 & \rho & \rho \\
\rho & \rho & 0 & 0 & 1 & \rho & \rho & \rho & \rho & 0 \\
\rho & 0 & \rho & 0 & \rho & 1 & \rho & \rho & 0 & \rho \\
\rho & 0 & 0 & \rho & \rho & \rho & 1 & 0 & \rho & \rho \\
0 & \rho & \rho & 0 & \rho & \rho & 0 & 1 & \rho & \rho \\
0 & \rho & 0 & \rho & \rho & 0 & \rho & \rho & 1 & \rho \\
0 & 0 & \rho & \rho & 0 & \rho & \rho & \rho & \rho & 1
\end{pmatrix}
\end{array}
$$

Multiple Testing Correction

- ***Two types of errors***
  - *What is H_0 in FMRI studies? H_0 = no effect (activation, difference, …) at a voxel*
  - *Type I error = Prob(reject H_0 when H_0 is true) = false positive = p value*
    - *Type II error = Prob(accept H_0 when H_1 is true) = false negative = β*
    - ***power** = 1−β = probability of detecting true activation*
  - *Goal: control type I error rate while increasing power (decreasing type II errors)*
  - *Significance level **α** (magic number 0.05) : $p < \alpha$*

Justice System: Trial

Hidden Truth

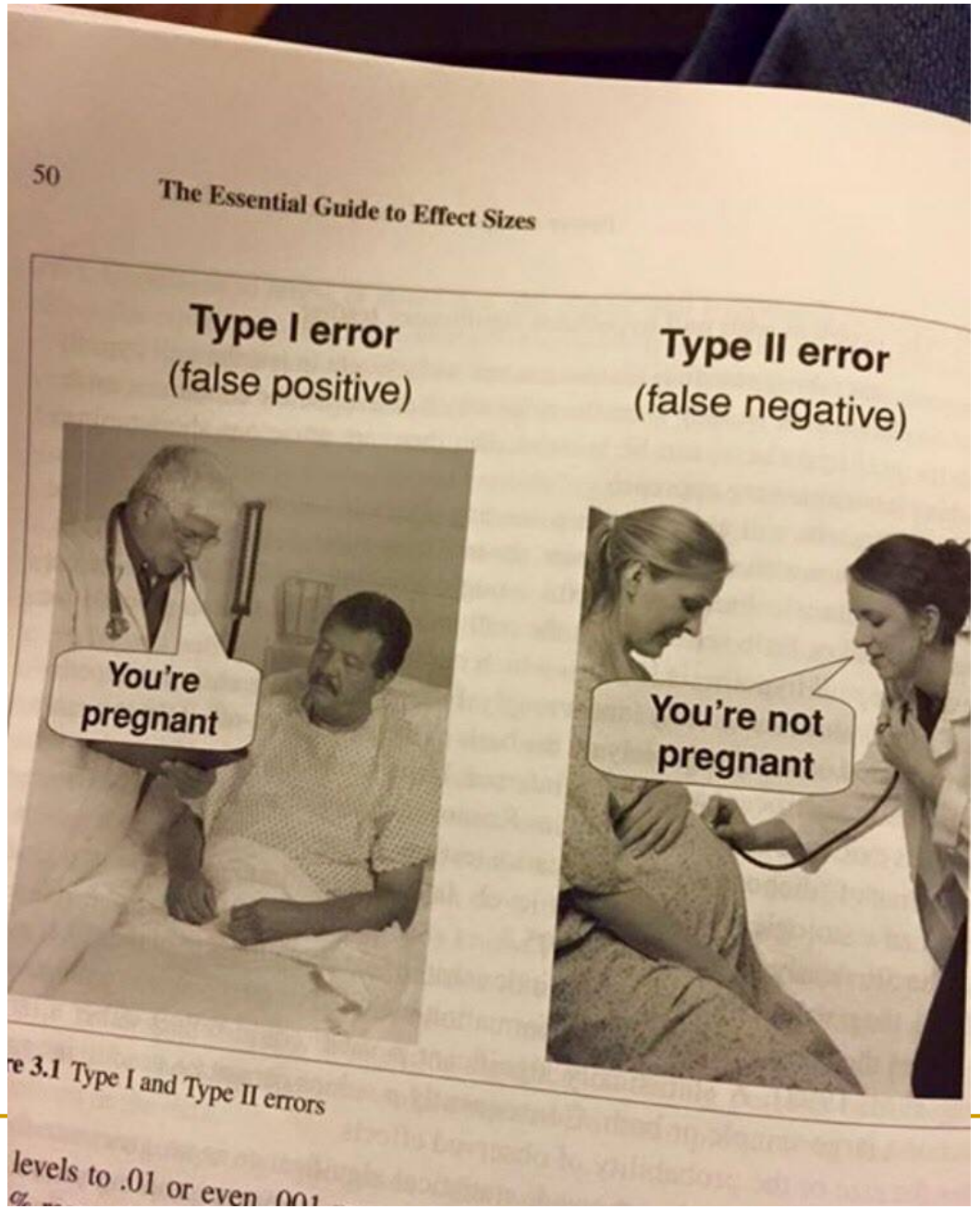
	Defendant Innocent	Defendant Guilty
Reject Presumption of Innocence (Guilty Verdict)	**Type I Error** (defendant very unhappy)	**Correct**
Fail to Reject Presumption of Innocence (Not Guilty Verdict)	**Correct**	**Type II Error** (defendant very happy)

Statistics: Hypothesis Test

Hidden Truth

	H_0 True Not Activated	H_0 False Activated
Reject H_0 (decide voxel is activated)	**Type I Error** (false positive)	**Correct**
Don't Reject H_0 (decide voxel isn't activated)	**Correct**	**Type II Error** (false negative)

Multiple Testing Correction



Multiple Testing Correction

- **Two types of correction**
  - Same test repeated many times (number of voxels)
    - Family-wise error (FWE)
    - Counterbalance between cluster size and voxel-wise significance
    - Difficulties: not to over-penalize yourself due to spatial correlation, but spatial structure is neither Gaussian nor homogeneous!
    - Correction via permutations with quantifying the counterbalance
  - Multiple tests in a study: six pairwise comparisons among four levels of a factor
    - Little attention in neuroimaging community

Miscellaneous

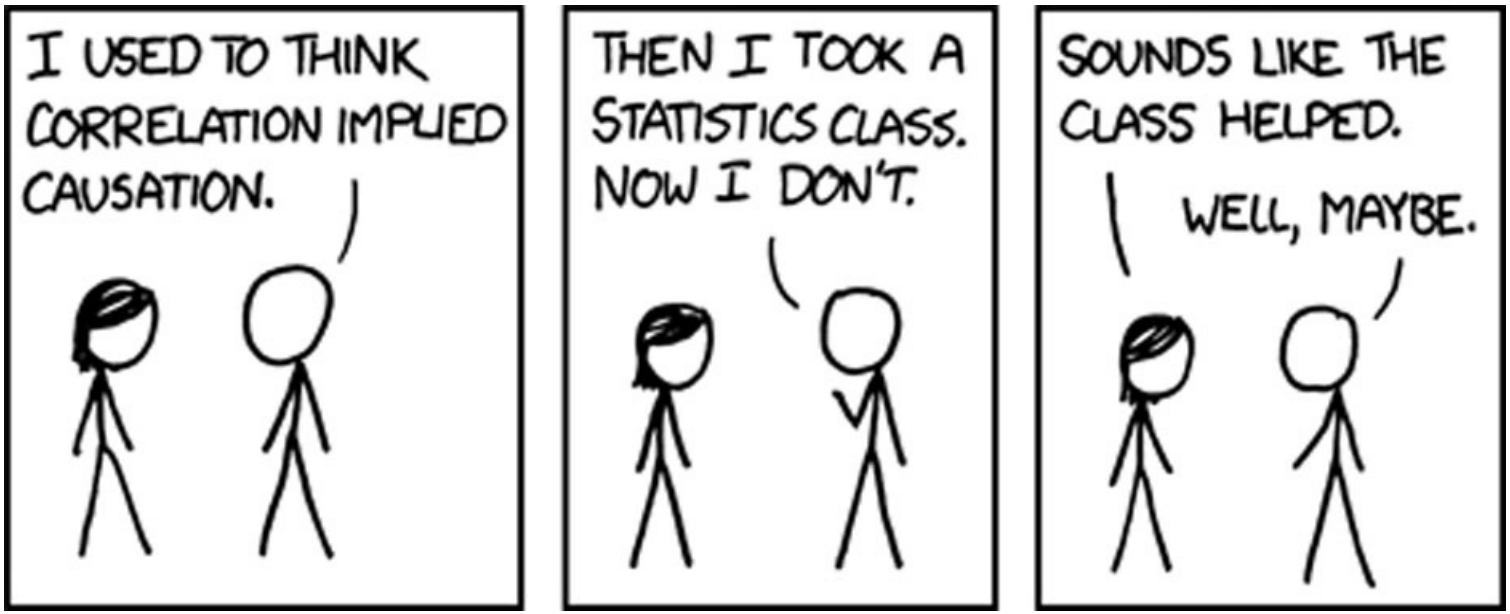
- Science is about reproducibility
  - Widespread obsession with *p*-values in FMRI
    - Colored blobs of *t*-values
    - Peak voxel selected based on peak *t*-value
  - **Unacceptable** in some fields if only *p*-value is reported
    - Basic and Applied Social Psychology bans p-value
    - Neuroimaging: an exception currently!
- 2-tier approach
  - Start with a liberal thresholding of *p*: 0.05 or even 0.1
  - Report rigorous results (multiple testing correction)
  - Also report the clusters under voxel-wise *p* of 0.05 but still have some spatial extent with some cautionary words

Miscellaneous

- Statistical significance (p-value) may become obsession
  - Published papers: Big and tall parents (violent men, engineers) have more sons, beautiful parents (nurses) have more daughters
  - P-hacking
- Two types of significance
  - Practical significance: lower cholesterol level by 2.7 mmol/L
  - Statistical significance
- Limitations of statistical inference
  - Binary decision: a statistically non-significant effect does not mean practically non-significant
  - The difference between a statistically significant effect and a non-significant one is not necessarily statistically significant

Miscellaneous

- Correlation vs. causation
  - Incidence of childhood leukemia: several times greater in certain Denver suburbs than in other parts of the country
    - High-voltage power lines?
  - Lots of correlation analysis in FMRI



Lastly

- Essentially all models are wrong, but some are useful. (George E. P. Box)

- Statistics are like a bikini. What they reveal is suggestive, but what they conceal is vital. (Aaron Levenstein)