Data Analysis: Modeling FMRI Signals and Noise

- Signal = Measurable response to stimulus

  Noise = Components of measurement that interfere with detection of signal

- Statistical detection theory:

  ◇ Must understand relationship between stimulus and signal

  ◇ Must characterize noise statistically

  ◇ Can then devise methods to distinguish noise-only measurements from signal+noise measurements, and assess their reliability

- FMRI signals and noise:

  ◇ Stimulus→signal and noise statistics are both poorly characterized

  ◇ Result is that there is no "best" way to analyze FMRI time series data: there are only "reasonable" analysis methods

  ◇ To deal with data, must make some assumptions about the signal and noise

  ◇ These assumptions will be wrong, but have to do something

  ◇ Different kinds of experiments require different kinds of analyses, since signal models and questions you ask about the signal will vary

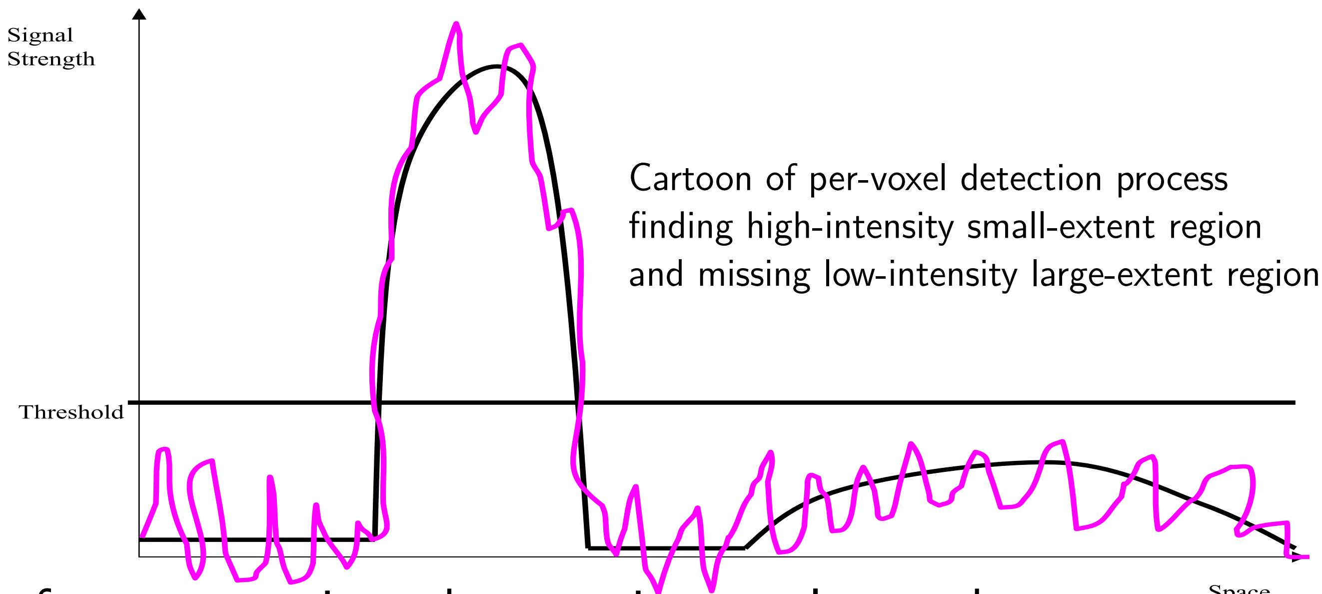
  ↪ Therefore it is important to understand what is going on, so you can select and evaluate "reasonable" analysis approaches

- Meta-method for generating analysis methods:
  - $\diamondsuit$ Write down a mathematical model connecting stimulus to signal
  - $\diamondsuit$ Write down a statistical model for the noise
  - $\diamondsuit$ Combine them to produce an equation for measurements given signal$+$noise (signal may have zero strength)
  - $\diamondsuit$ Use statistical detection theory to produce an algorithm for processing the measurements to assess signal presence and characteristics
- Fundamental difficulty with neuroimaging data: don't have enough measurements
  - $\diamondsuit$ Sounds crazy: typically get $\frac{1}{2}$ Gbyte of data per scanning sesssion
  - $\diamondsuit$ But most of this is not relevant to neural activity (BOLD signal is weak)
  - $\diamondsuit$ Must make <u>many</u> decisions to make a brain map: at least one per voxel
    - $\hookrightarrow$ Typically have $10^4 \ldots 10^5$ voxels in the brain
    - $\hookrightarrow$ If chance of making a mistake in any one voxel is 1% ($p = 0.01$), then expect $100 \ldots 1000$ errors in every brain map
    - $\hookrightarrow$ This may be as big as the number of truly active voxels in the brain $\Rightarrow$ results are garbage

◇ There are two ways out of this multiple comparisons problem:

↪ Make the p-value per voxel much more stringent (smaller), so that the number of expected errors goes way down

▷ Problem: Low-intensity large-extent activations will be tossed out



Cartoon of per-voxel detection process finding high-intensity small-extent region and missing low-intensity large-extent region

↪ Make fewer comparisons by grouping voxels together

▷ Spatial smoothing of the data prior to detection (à la PET analyses)

▷ Analyze data only after averaging over regions-of-interest (ROIs)

▷ Two-step detection (spatial clustering):

- Provisionally accept as active voxels above some threshold signal level
- Finally accept only voxels contiguous with other supra-threshold voxels
- Isolated "salt and pepper noise" activations are excised

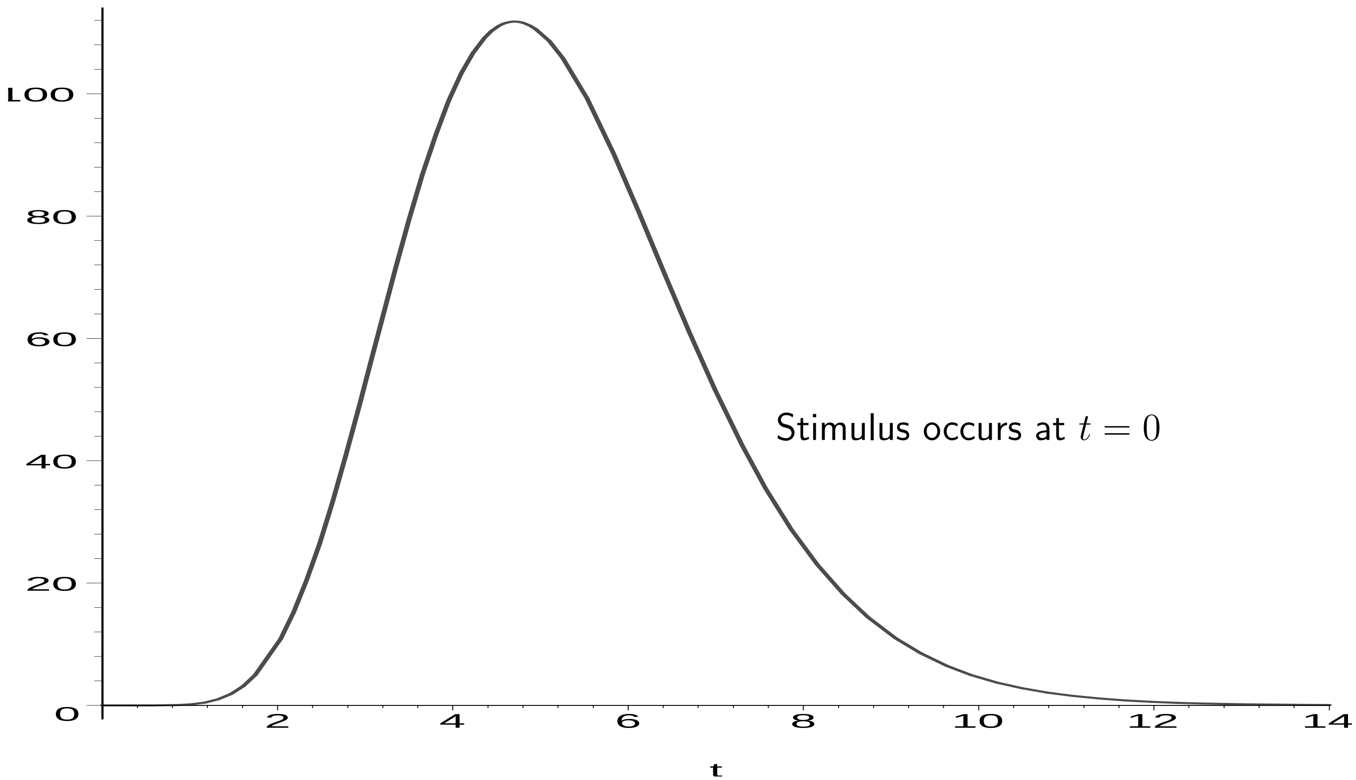
▷ Problem: Loss of spatial resolution

- Mathematical theory follows:
  - ◇ Will try to follow notation Doug Ward used in his manual for `3dDeconvolve`
  - ◇ Time occurs continuously in reality, but in steps in data acquisition
    - ↪ Functions of continuous time are expressed like $f(t)$
    - ↪ Functions of discrete time are expressed like $f(n\Delta t)$, where $n = 0, 1, 2, \ldots$ and $\Delta t =$ time step (also called TR in MRI)
    - ↪ May also use subscript notation f_n to mean same thing as $f(n\Delta t)$
    - ↪ A collection of numbers assembled in a column is a vector and is printed in boldface, as in

$$\begin{bmatrix} f_0 \\ f_1 \\ f_2 \\ \vdots \\ f_M \end{bmatrix} = \mathbf{f} \qquad (\underline{\mathrm{f}} \text{ in handwriting})$$

- Will begin with simple case, and work upward to models that are realistic for complex neuropsychological experiments

- Model for signal: Known and fixed response to each stimulus
  - ◇ Example: response function $\boldsymbol{h(t) = t^{8.6} e^{-t/0.547}}$ (Mark Cohen)



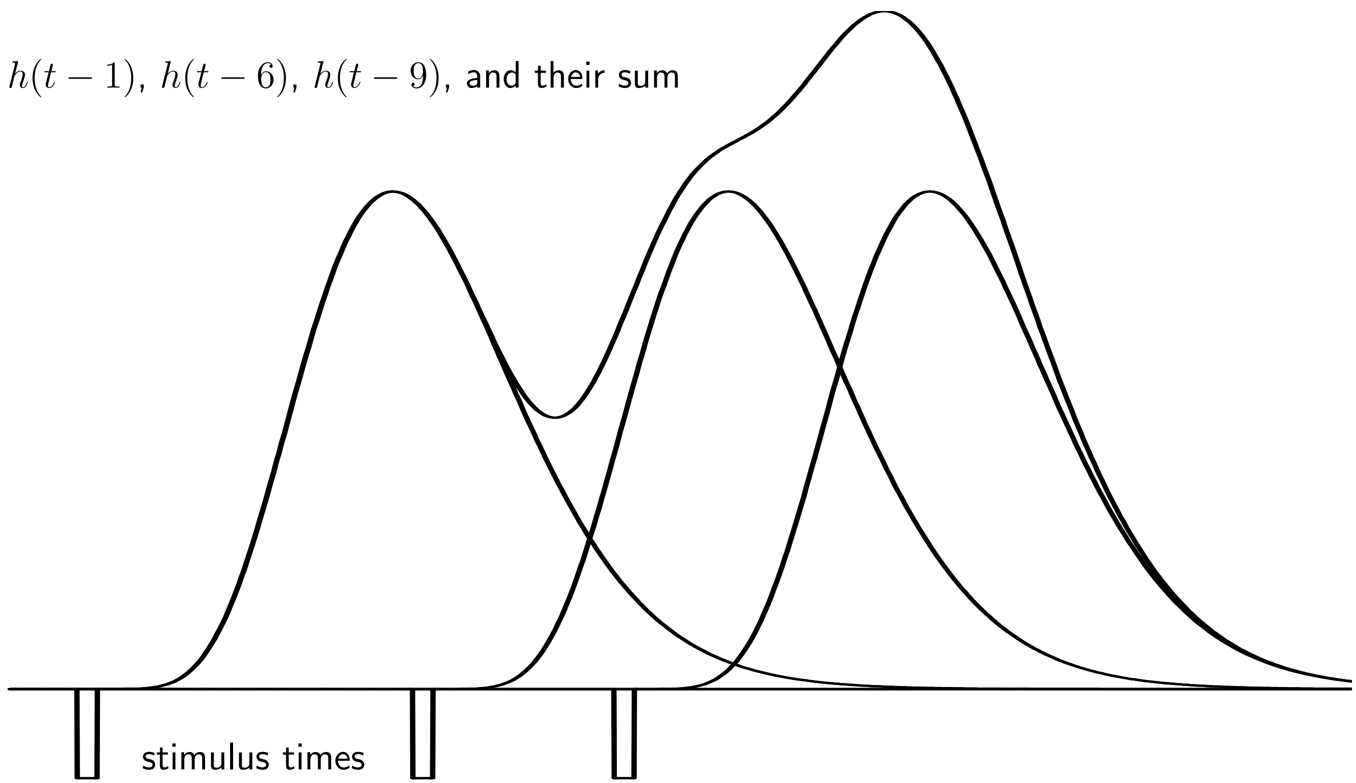
  - ◇ Response model starts at and returns to 0, so final measurement model must additionally include a baseline for each voxel
  - ◇ Stimuli are encoded by a time series that is either 0 or 1 at each point:

$$f_n = \frac{\begin{array}{cccccccccccccc} 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 1 & 1 & \ldots \end{array}}{\begin{array}{ccccccccccccccc} t: & 0 & \Delta t & 2\Delta t & 3\Delta t & 4\Delta t & 5\Delta t & 6\Delta t & 7\Delta t & 8\Delta t & 9\Delta t & 10\Delta t & 11\Delta t & 12\Delta t & \ldots \end{array}}$$

◇ Idealized response to this sequence of stimuli is convolution of individual response function $h(t)$ with stimulus function $f(t)$:

$$r_n = f_n \cdot h_0 + f_{n-1} \cdot h_1 + f_{n-2} \cdot h_2 + \cdots + f_{n-p} \cdot h_p = \sum_{m=0}^{p} f_{n-m} \cdot h_p$$

↪ The response at time $n\Delta t$ is the sum of responses from previous stimuli



↪ We assume that BOLD-derived MRI signals are strictly additive

▷ Only approximately true, but this assumption is widely used

▷ AFNI program `waver` can compute r_n timeseries, given f_n

$\hookrightarrow$ The maximum convolution lag p determines how far into the future an individual stimulus reaches: $p\Delta t \approx (10 + D)$s for neural activity lasting D seconds

$\diamond$ A simple experiment: only two types of conditions (e.g., rest and stimulus)

$\hookrightarrow$ AFNI interactive `FIM` and `FIM+` handle this case (in graph window)

$\hookrightarrow$ Measurement model for each voxel separately:

$$Z_n = \beta_0 + \beta_1 \cdot n + \alpha \cdot r_n + \varepsilon_n$$

$$\begin{aligned} \text{where} \quad Z_n &= \text{measured value at time } t = n\Delta t \\ \beta_0 &= \text{baseline} \\ \beta_1 &= \text{baseline drift rate (or trend)} \\ \alpha &= \text{amplitude of response} \\ \varepsilon_n &= \text{measurement noise (zero mean) in } n^{\text{th}} \text{ sample} \\ n &= 0, 1, 2, \ldots, N-1 \quad \text{(there are } N \text{ measurements in time)} \end{aligned}$$

$\hookrightarrow$ In this model, there are 4 parameters we don't know (in each voxel): β_0, β_1, α, and σ^2 = noise variance

- $\triangleright$ We know $h(t)$ = individual response function and $f(t)$ = stimulus time series, so we know $r(t)$ as well
- $\triangleright$ β_0 and β_1 are "nuisance parameters" in the measurement model: we don't usually care what they are, but must include them to be realistic

- $\hookrightarrow$ This model is called linear since the unknown parameters β_0, β_1, α appear only by multiplying quantities we know (1, n, r_n, respectively)
  - ▷ Linear models are nice, since the algorithms for calculating results from them are relatively straightforward
- $\hookrightarrow$ We can calculate estimates of β_0, β_1, α using the method of linear least squares: minimize the sum E

$$E = \sum_{n=0}^{N-1} \left[Z_n - (\beta_0 + \beta_1 \cdot n + \alpha \cdot r_n)\right]^2$$

  over all possible values of β_0, β_1, α
  - ▷ We do this because we expect $Z_n \approx \beta_0 + \beta_1 \cdot n + \alpha \cdot r_n$
  - ▷ Estimates of the true (unknowable) parameters are denoted with a "hat", as in $\hat{\beta}_0$, $\hat{\beta}_1$, $\hat{\alpha}$
  - ▷ Statistical estimation theory lets us also estimate $\hat{\sigma}^2$ from the minimized value of E
  - ▷ Then also can estimate accuracy of the parameter estimates
- $\hookrightarrow$ Activation detection: is $\alpha \neq 0$? (or, is there any response to stimulation?)
  - ▷ Essentially, we determine if $\hat{\alpha}$ is "far enough" away from 0 to make it very unlikely that the true $\alpha = 0$
  - ▷ "Far enough" is determined by the estimation accuracy

▷ Must make some assumptions about the statistical distribution of the noise

- Gaussian distribution is almost always assumed
- Stationary in time is almost always assumed
- Can assume noise is "white" (uncorrelated in time), or
- Can assume noise is temporally correlated, and try to estimate that as well

▷ In practice, activation decision is computed by first computing an intermediate statistic, which is then thresholded to make the final decision

- F-, t-, and correlation coefficient statistics are all used
- In this simple case (only 1 activation parameter α), these are equivalent
- Significance and power of test depend on distribution of noise

▷ AFNI interactive `FIM` and `FIM+` compute correlation coefficient statistic

- $\hat{\rho}^2$ is the fraction of the variance in the detrended signal

$$Z_n - \hat{\beta}_0 - \hat{\beta}_1 \cdot n$$

that is explained by the component $\hat{\alpha} \cdot r_n$

- If true $\alpha = 0$, and if noise is white, $\hat{\rho}^2$ follows Beta distribution
- If noise is correlated in time, $\hat{\rho}^2$ distribution is very complex
- Can approximate with a Beta distribution, but must estimate parameters
- After have a statistic with a known distribution, can threshold it at a given p-value