Practical Experimental Design for fMRI

Thomas Nichols

with Rik Henson & Kent Kiehl

Five Guidelines for fMRI Design

1) Scan as many subjects as possible; scan as long as participants can accommodate

2) Keep blocks short; long blocks (>40 seconds) confound low-frequency noise

3) Limit the number of conditions; pairwise comparisons far apart in time may be confounded by low-frequency noise

4) Randomize the ordering of events that are close together in time

5) Randomize SOA between events that need to be distinguished (decorrelate their effects after HRF convolution)

1) Scan as many subjects as possible; scan as long as participants can accommodate

1) The bane of imaging studies is small sample sizes – leads to false positives and false negatives – too much power is never enough!

2) Scan participants for as long as you can – without them getting fatigued or bored – which can lead to excessive motion, poor performance, or having to pee!

3) Scan long enough to derive an accurate estimate of the conditions of interest! Average 6-12 minutes per run and up to 4 runs per participant

Epoch vs Events

- Epochs are periods of sustained stimulation (e.g, box-car functions)
- Events are impulses (delta-functions)
- Near-identical regressors can be created by:

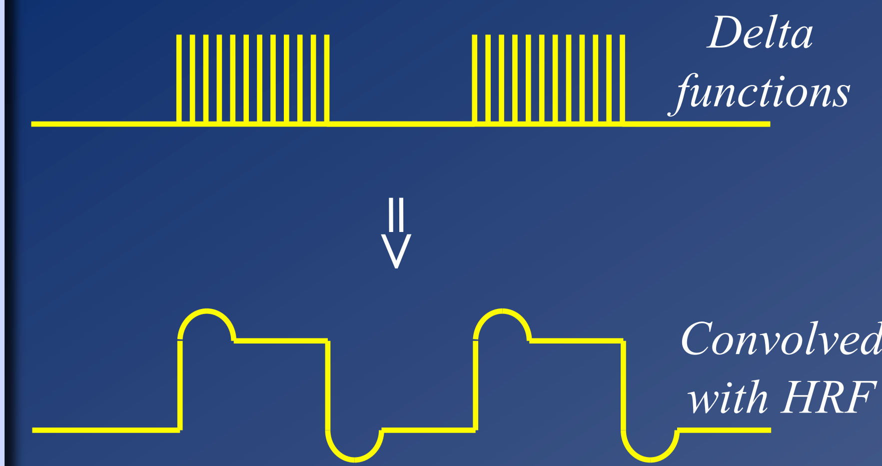
    1) sustained epochs

    2) rapid series of events (SOAs<~3s)

- i.e, *designs* can be blocked or intermixed … *models* can be epoch or event-related

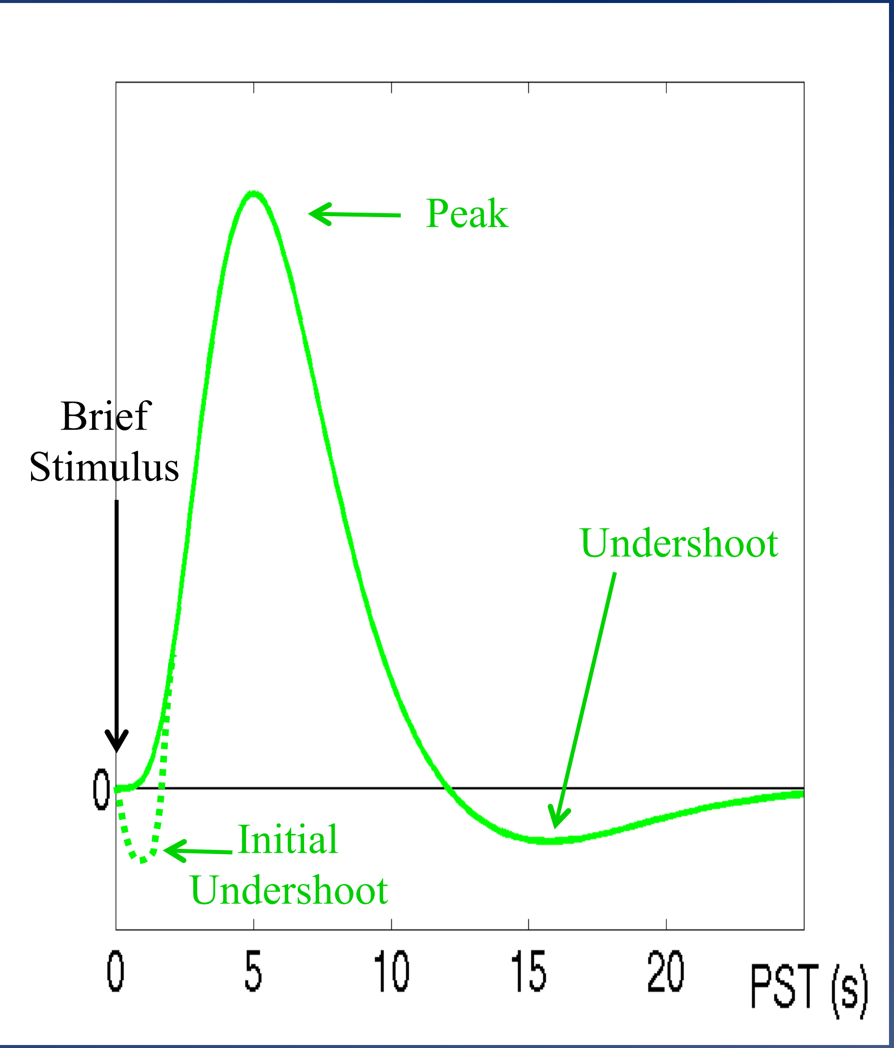
Sustained epoch

Blocks of events



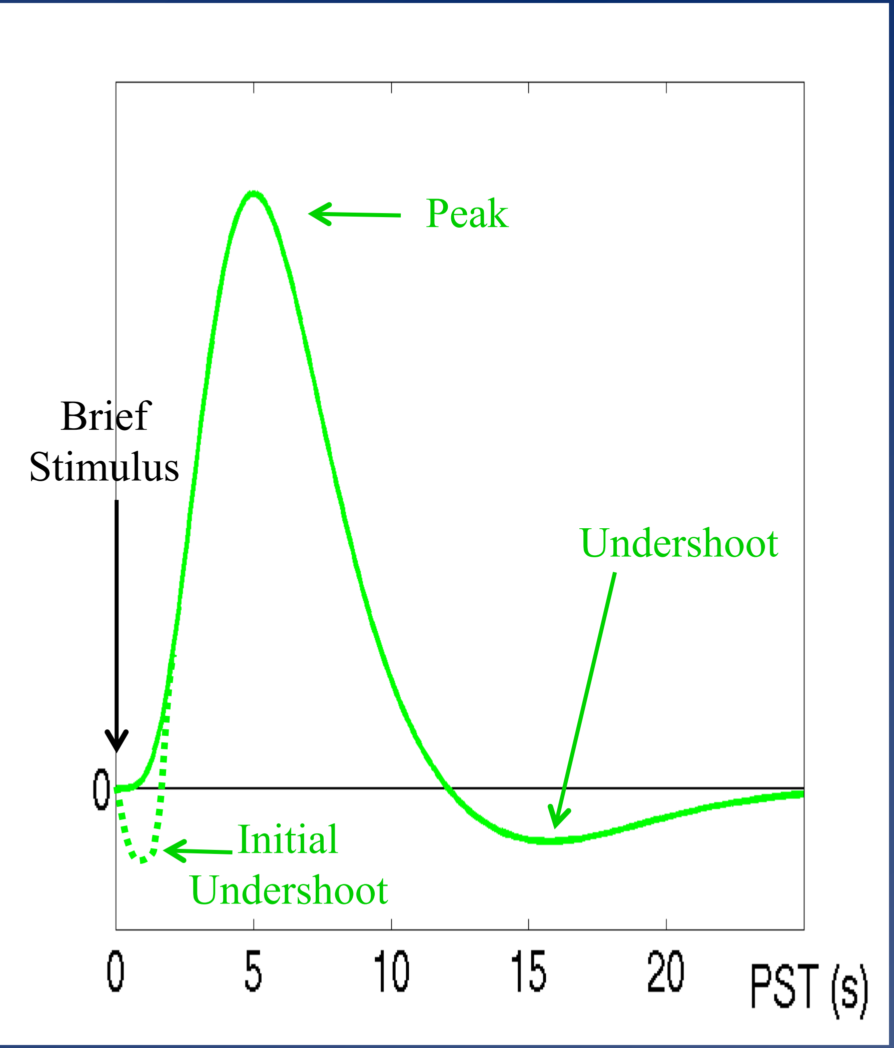
BOLD Impulse Response

- Function of blood oxygenation, flow, volume (Buxton et al, 1998)
- Peak (max. oxygenation) 4-6s poststimulus; baseline after 20-30s
- Initial undershoot can be observed (Malonek & Grinvald, 1996)
- Similar across V1, A1, S1…
- … but differences across:
  other regions (Schacter et al 1997)
  individuals (Aguirre et al, 1998)



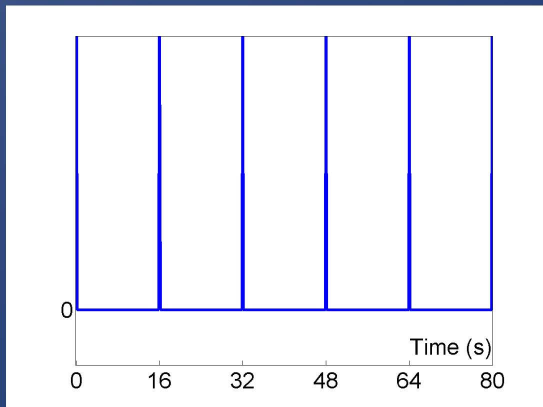
BOLD Impulse Response

- Early event-related fMRI studies used a long Stimulus Onset Asynchrony (SOA) to allow BOLD response to return to baseline
- However, if the BOLD response is explicitly modeled, overlap between successive responses at short SOAs can be accommodated…
- … particularly if responses are assumed to superpose linearly
- Short SOAs are more sensitive…



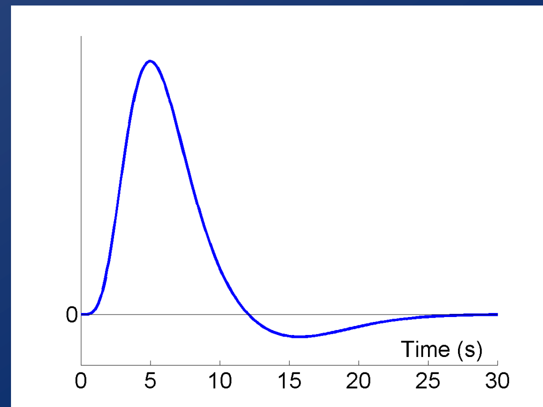
Fixed SOA = 16s

Stimulus (“Neural”)



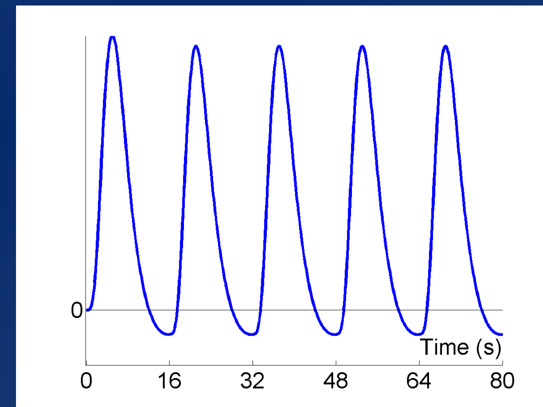
$\otimes$

HRF



=

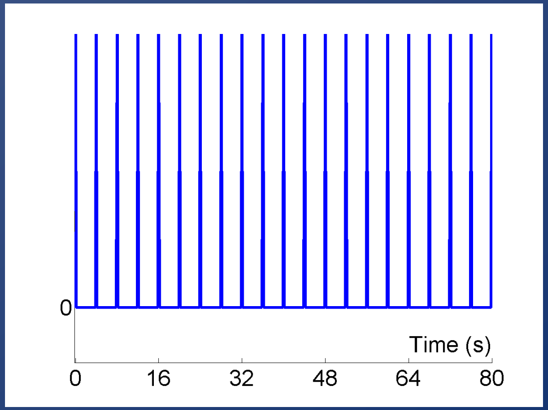
Predicted Data



Not particularly efficient…

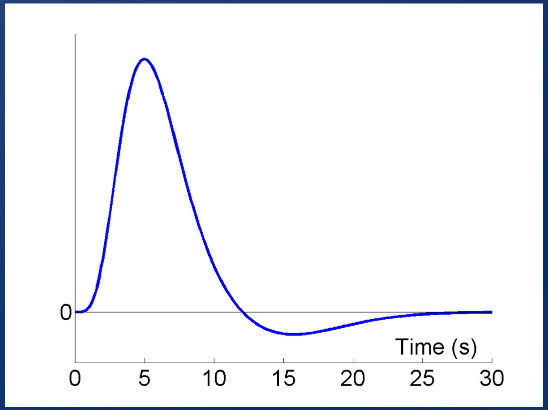
Fixed SOA = 4s

Stimulus ("Neural")



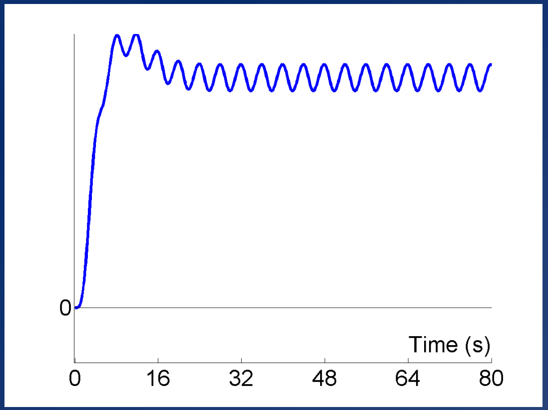
$\otimes$

HRF



$=$

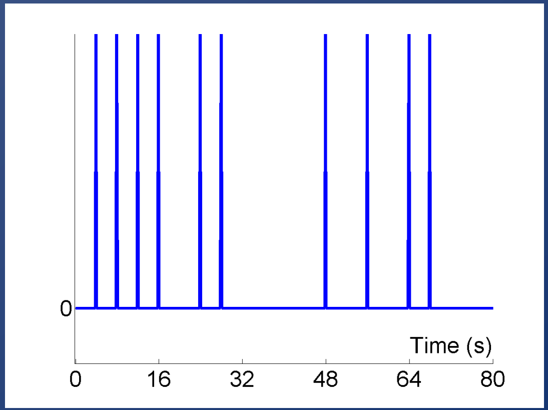
Predicted Data



Very Inefficient…

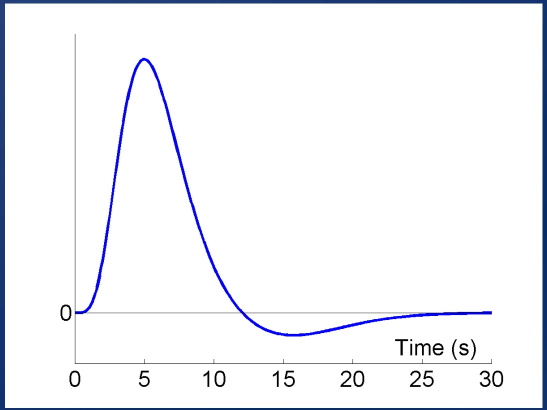
Randomised, SOA$_{min}$ = 4s

Stimulus ("Neural")



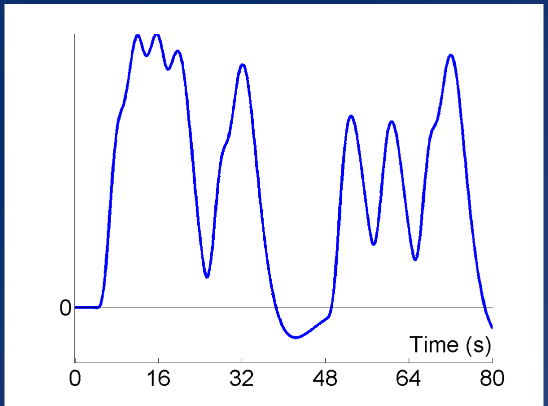
$\otimes$

HRF



=

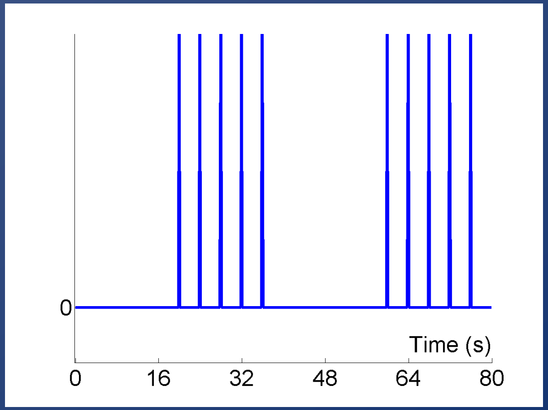
Predicted Data



More Efficient…

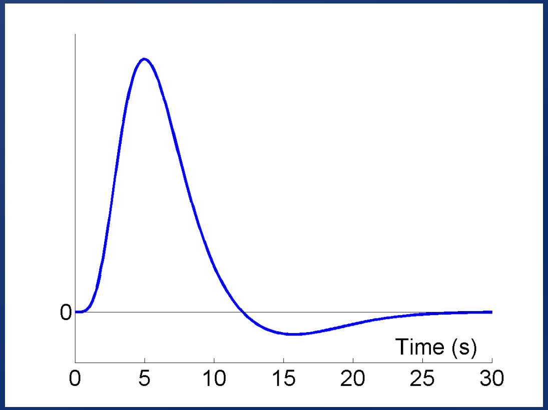
Blocked, SOA_{min} = 4s

Stimulus (“Neural”)



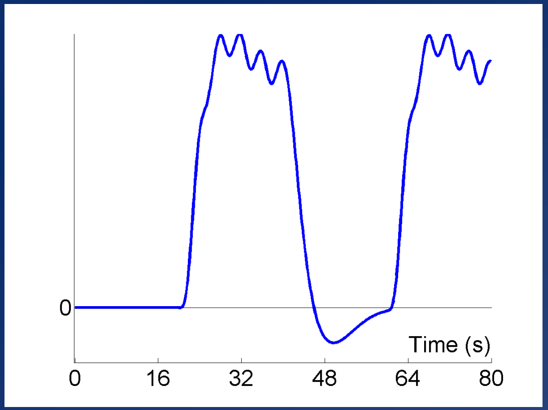
⊗

HRF



=

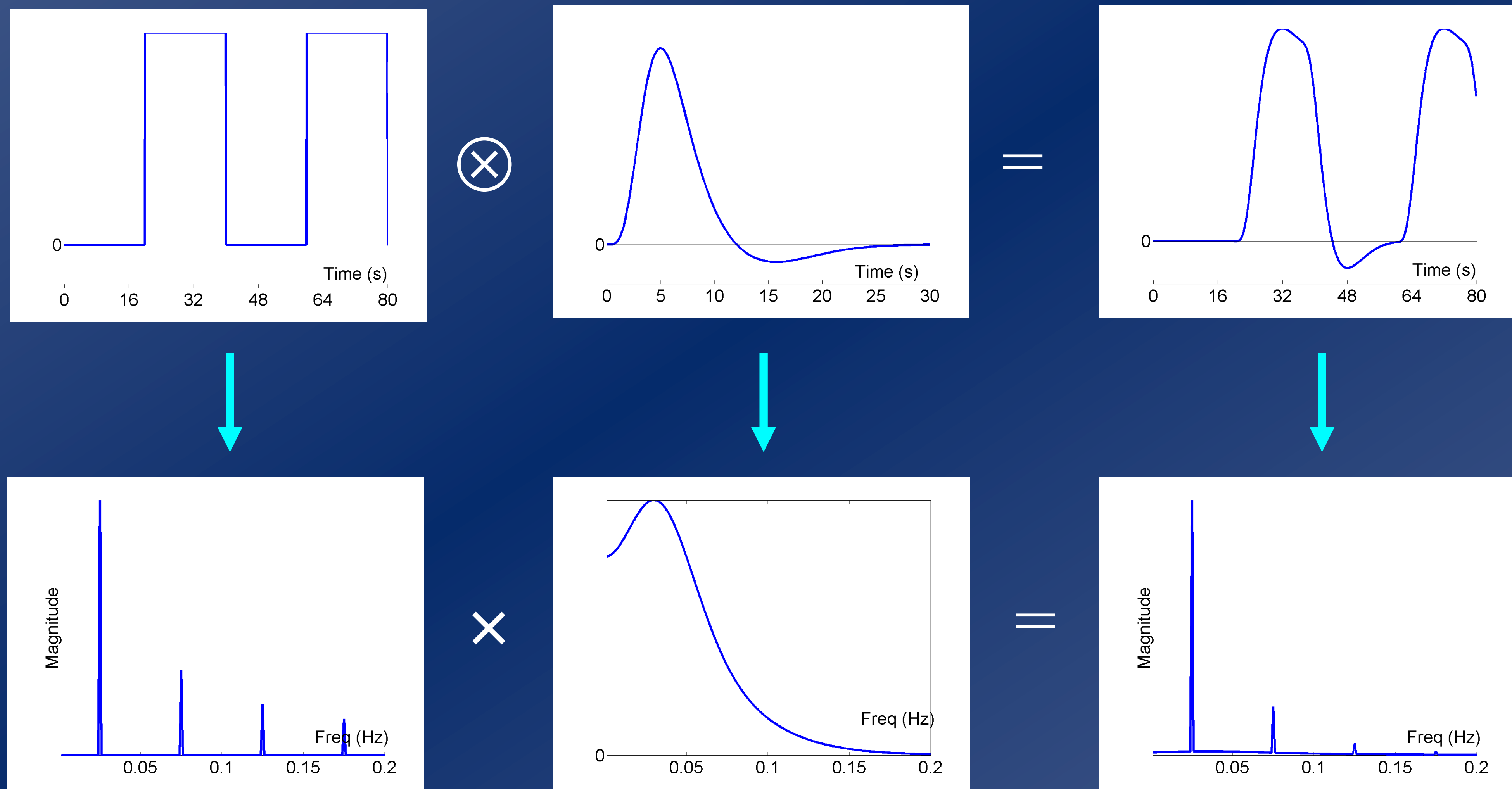
Predicted Data



Even more Efficient…

Blocked, epoch = 20s

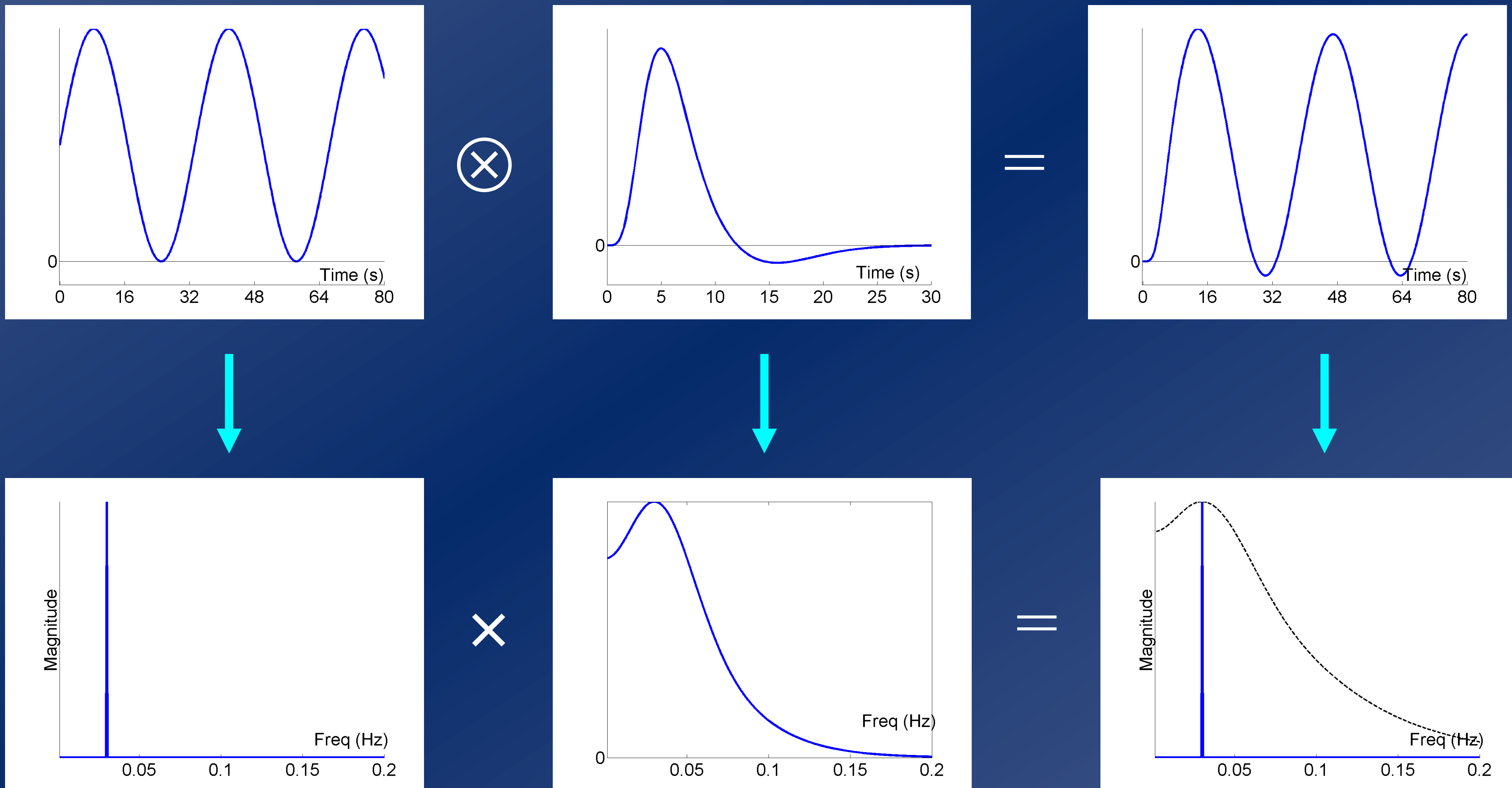
Stimulus (“Neural”) HRF Predicted Data



Blocked-epoch (with small SOA) and Time-Freq equivalences

Sinusoidal modulation, f = 1/33s

Stimulus ("Neural") HRF Predicted Data

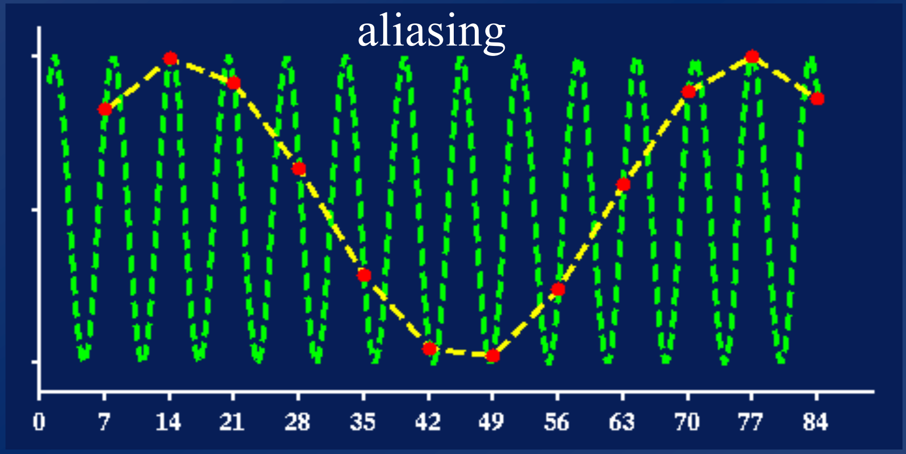


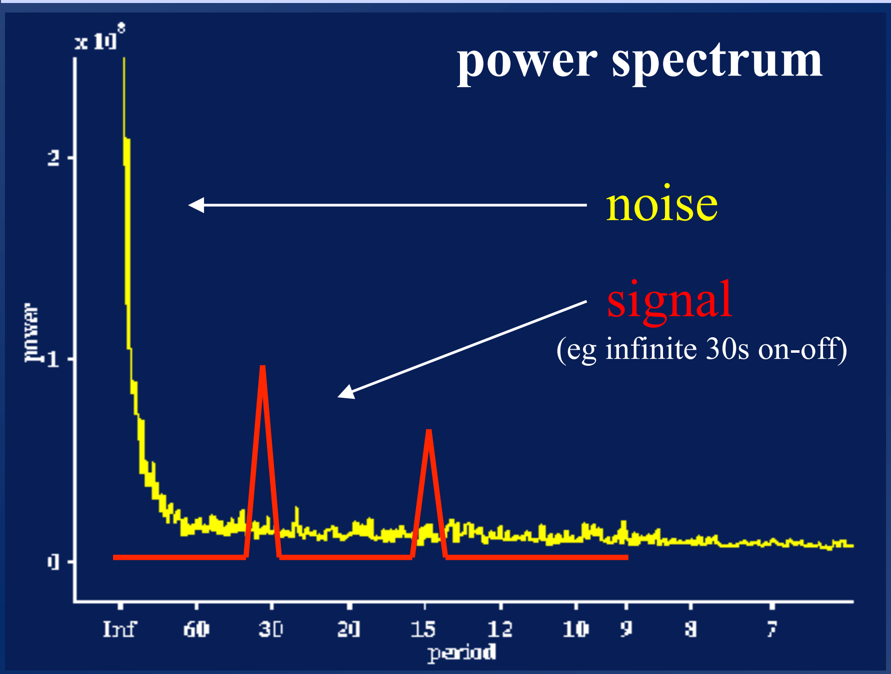
The most efficient design of all!

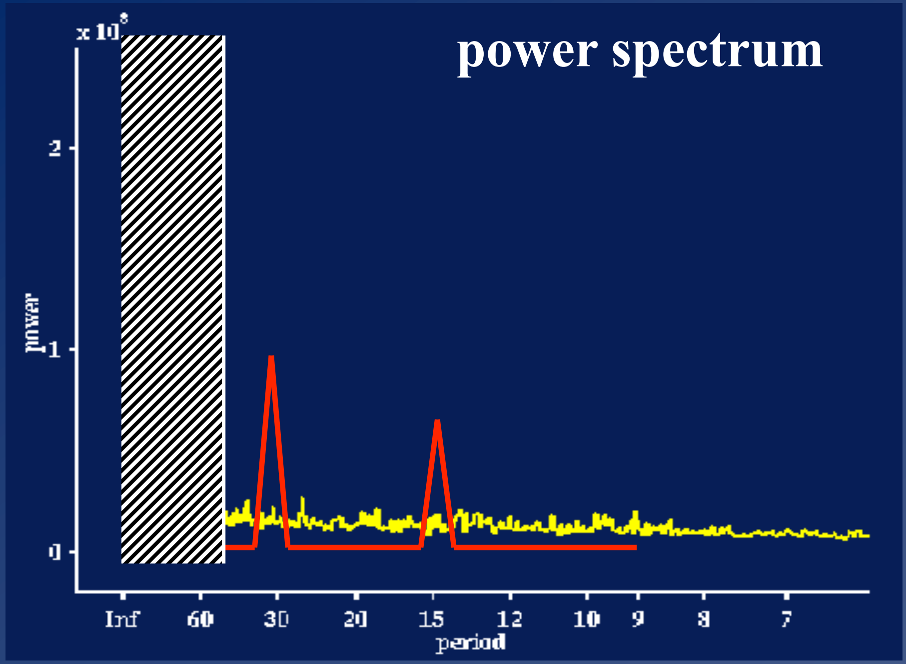
High-pass Filtering

fMRI contains low frequency noise:

- Physical (scanner drifts)
- Physiological (aliased)
  - cardiac (~1 Hz)
  - respiratory (~0.25 Hz)

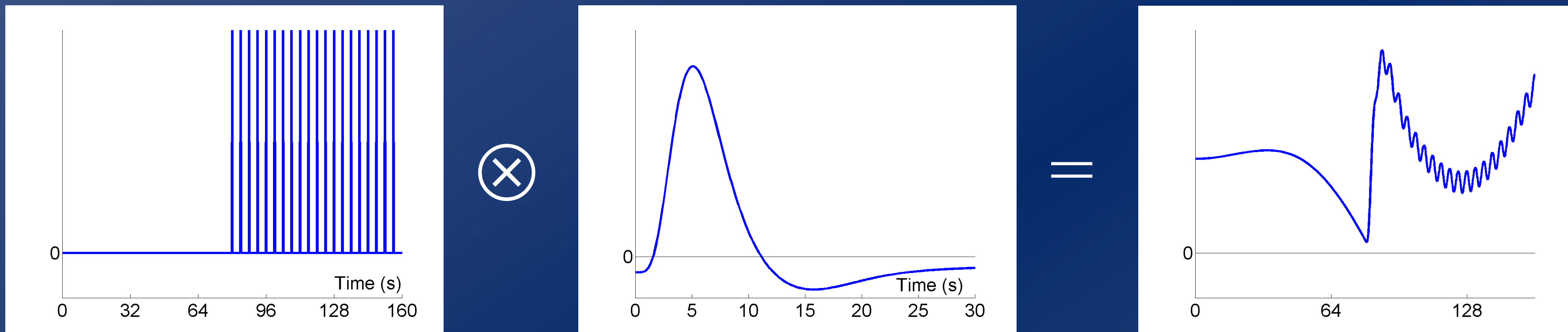




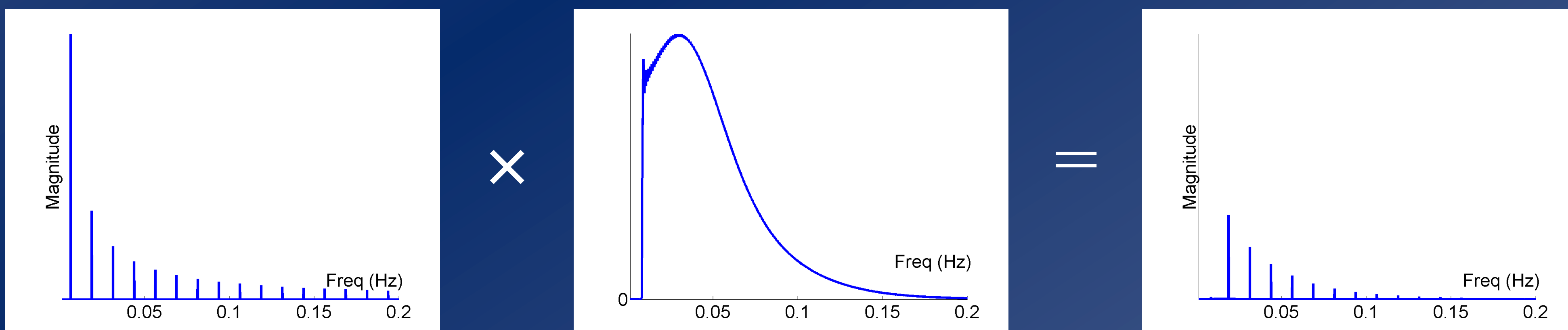


Blocked (80s), SOA_{min}=4s, highpass filter = 1/120s

Stimulus ("Neural") HRF Predicted Data



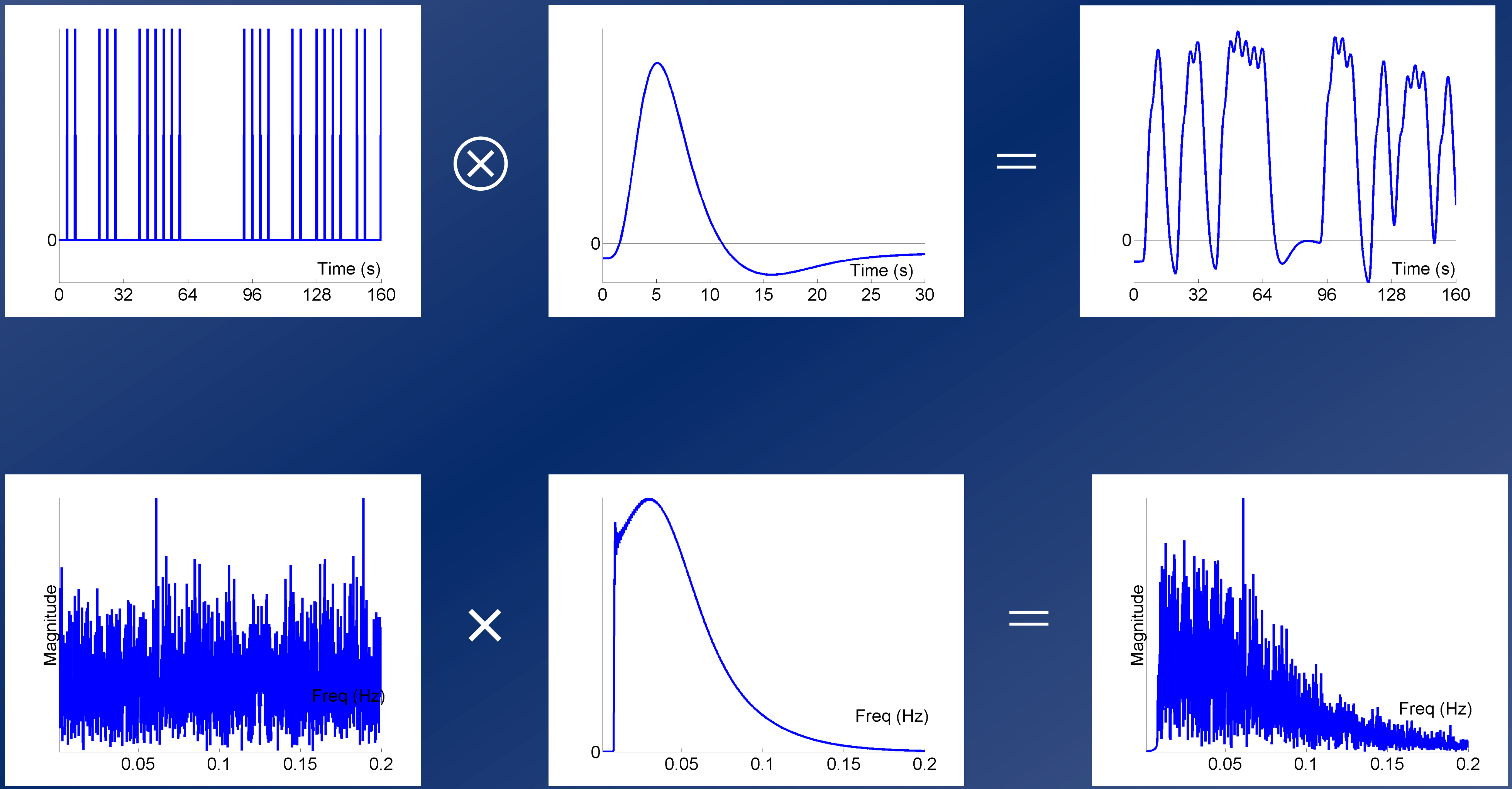
"Effective HRF" (after highpass filtering)
(Josephs & Henson, 1999)



Don't have long (>60s) blocks!

Randomised, SOA_{min}=4s, highpass filter = 1/120s

Stimulus (“Neural”) HRF Predicted Data



(Randomised design spreads power over frequencies)

Advantages of Event-related models

1. Randomized (intermixed) trial order
   c.f. confounds of blocked designs (Johnson et al 1997)

2. Post hoc / subjective classification of trials
   e.g, according to subsequent memory (Wagner et al 1998)

3. Some events can only be indicated by subject (in time)
   e.g, spontaneous perceptual changes (Kleinschmidt et al 1998)

4. Some trials cannot be blocked
   e.g, "oddball" designs (Kiehl et al 2000a;b;2005a,b)

5. More accurate models even for blocked designs?
   e.g, "state-item" interactions (Chawla et al 1999)

Long 'Effective' SOA

- Example design:

  => A B B A B B A B A A ... 30 seconds per condition

- This means that the average SOA for the two conditions are:
  - A: 90+90+60+30/4 = 67.5 seconds
  - B: 30+60+30+60/4 = 45.0 seconds

  - Estimating condition B is more efficient than estimating condition A – when you consider the high-pass filter!

Five Guidelines for fMRI Design

1) Scan as many subjects as possible; scan as long as participants can accommodate

2) Keep blocks short; long blocks (>40 seconds) confound low-frequency noise

3) Limit the number of conditions; pairwise comparisons far apart in time may be confounded by low-frequency noise

4) Randomize the ordering of events that are close together in time

5) Randomize SOA between events that need to be distinguished (decorrelate their effects after HRF convolution)

A bit more formally… "Efficiency"

- The T-statistic (in GLM) is given by:

$$T = \mathbf{c}^T\hat{\beta} \,/\, \sqrt{\mathrm{var}(\mathbf{c}^T\hat{\beta})}$$

$$\mathrm{var}(\mathbf{c}^T\hat{\beta}) = \hat{\sigma}^2\, \mathbf{c}^T(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{c} \qquad \textit{(assuming i.i.d errors)}$$

where **c** is a "contrast", $\hat{\beta}$ are "parameter estimates", **X** is the "design matrix" and $\hat{\sigma}^2$ is the estimated noise variance

- For max T, want min contrast variability $\mathrm{var}(\mathbf{c}^T\hat{\beta})$ (Friston et al, 1999)

- If assume that noise variance (σ^2) is unaffected by changes in **X**…

- …then want maximal efficiency, e:

$$e(\mathbf{c},\mathbf{X}) = \{\, \mathbf{c}^T (\mathbf{X}^T\mathbf{X})^{-1}\, \mathbf{c} \,\}^{-1} \qquad \textit{(highpass filter part of X)}$$

Efficiency - Multiple Event-types

- Design parametrised by:

  SOA_{min} Minimum SOA

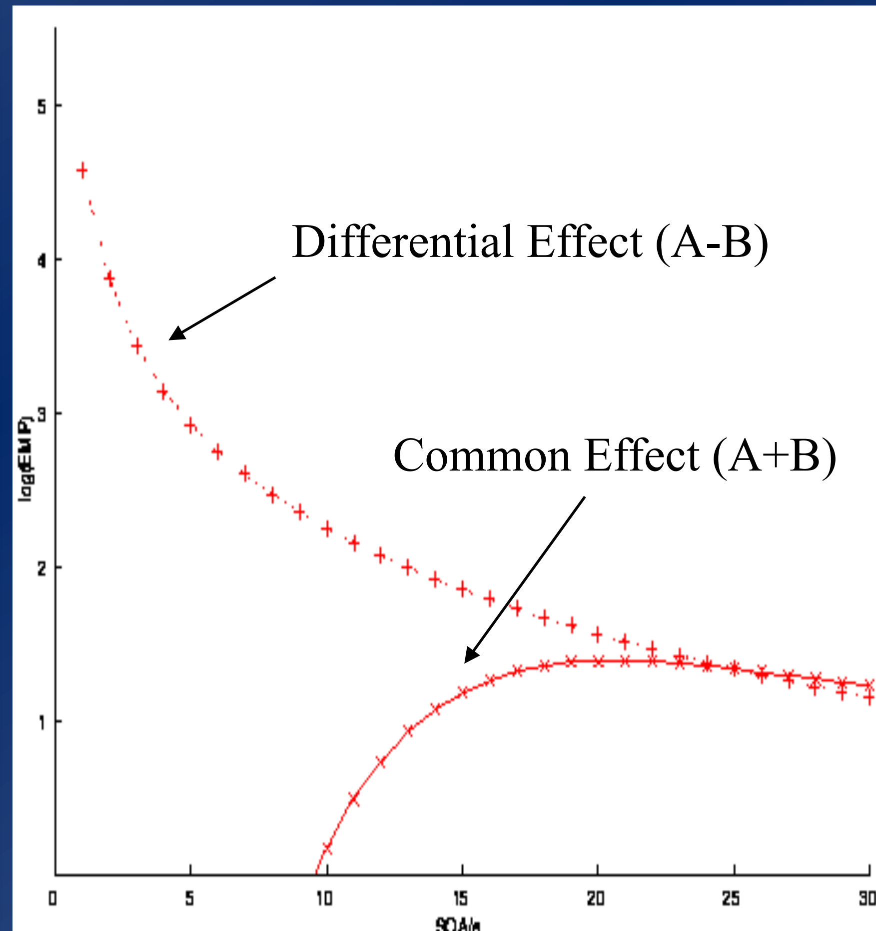
  $p_i(\boldsymbol{h})$ Probability of event-type i given history $\boldsymbol{h}$ of last m events

- With n event-types $p_i(\boldsymbol{h})$ is a $n^m \times n$ *Transition Matrix*

- Example: Randomised AB

	A	**B**
A	0.5	0.5
B	0.5	0.5

=> **ABBBABAABABAAA...**



4s smoothing; 1/60s highpass filtering

Efficiency - Multiple Event-types

- Example: Alternating AB

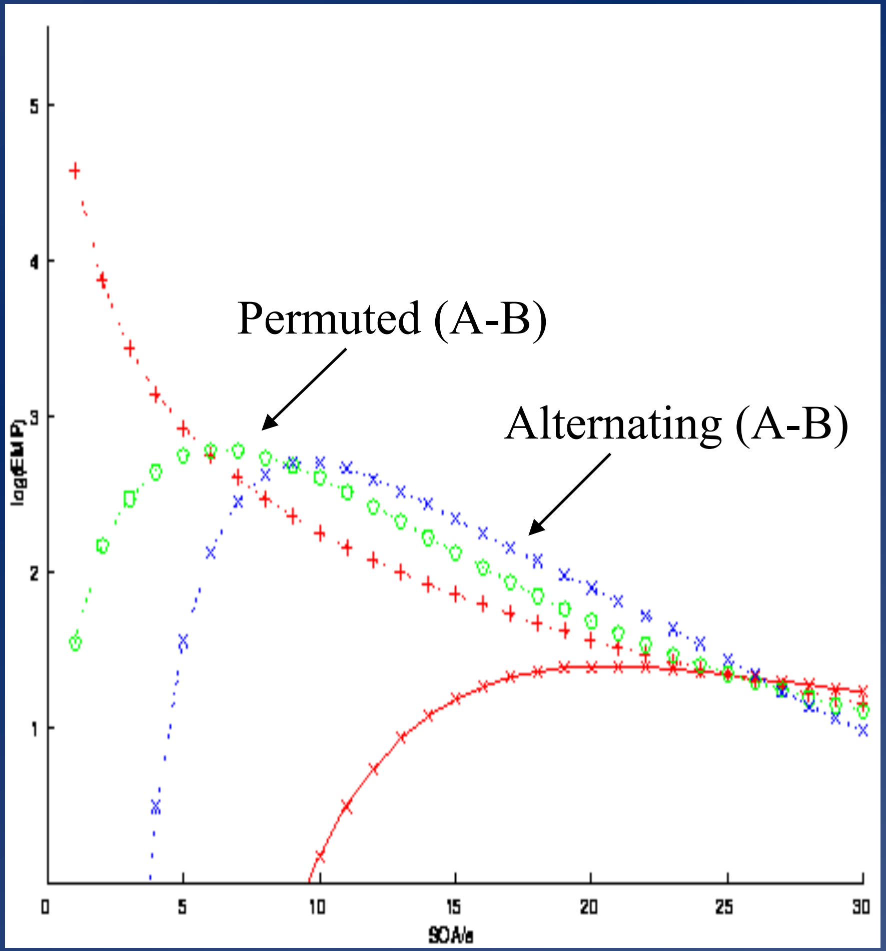
	A	**B**
A	0	1
B	1	0

=> **ABABABABABAB...**

- Example: Permuted AB

	A	**B**
AA	0	1
AB	0.5	0.5
BA	0.5	0.5
BB	1	0

=> **ABBAABABABBA...**



4s smoothing; 1/60s highpass filtering

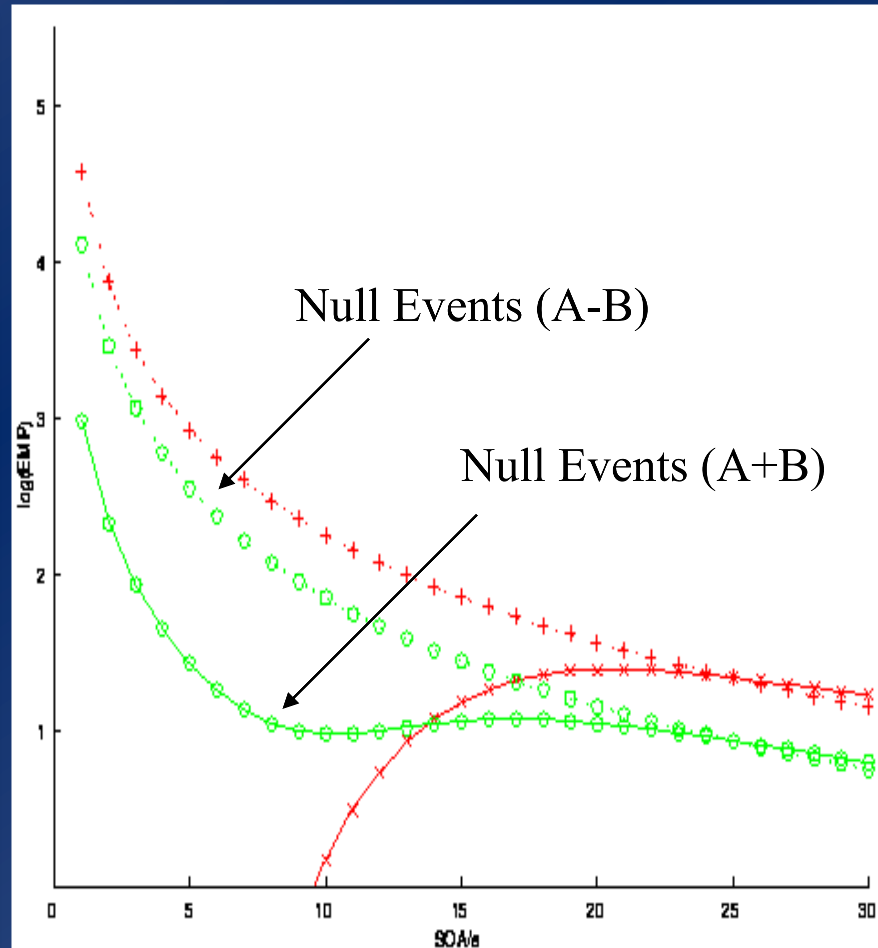
Efficiency - Multiple Event-types

- Example: Null events

	A	B
A	0.33	0.33
B	0.33	0.33

=> **AB-BAA--B---ABB...**

- Efficient for differential ***and*** main effects at short SOA
- Equivalent to stochastic SOA (Null Event like third unmodelled event-type)
- Selective averaging of data (Dale & Buckner 1997)



4s smoothing; 1/60s highpass filtering

Five Guidelines for fMRI Design

1) Scan as many subjects as possible; scan as long as participants can accommodate
2) Keep blocks short; long blocks (>40 seconds) confound low-frequency noise
3) Limit the number of conditions; pairwise comparisons far apart in time may be confounded by low-frequency noise
4) Randomize the ordering of events that are close together in time
5) Randomize SOA between events that need to be distinguished (decorrelate their effects after HRF convolution)

Efficiency - Conclusions

- Optimal design for one contrast may not be optimal for another
- Blocked designs generally most efficient with short SOAs (≈30s) (but with problems of interpretation, eg context-sensivity…)
- With randomised designs, optimal SOA for differential effect (A-B) is minimal SOA (assuming no saturation), whereas optimal SOA for main effect (A+B) is 16-20s
- Inclusion of null events improves efficiency for main effect at short SOAs (at cost of efficiency for differential effects)
- If order constrained, intermediate SOAs (5-20s) can be optimal; If SOA constrained, pseudorandomised designs can be optimal (but may introduce context-sensitivity)

The End

For further info on how to design an efficient fMRI experiment, see:

http://www.mrc-cbu.cam.ac.uk/Imaging/Common/fMRI-efficiency.shtml