# Introduction à la statistique médicale

# Statistical Parametric Mapping short course

<u>Course 5:</u>

Evoked response fMRI &
Design efficiency

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GIGA – *In Silico* Medicine

LIÈGE université GIGA CRC In vivo Imaging

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# Content

- Block/epoch vs. event-related fMRI
- (Dis)Advantages of efMRI
- GLM: Convolution
- BOLD impulse response
- Temporal Basis Functions
- Timing Issues
- Design Optimisation – "Efficiency"

# Content

- **Block/epoch vs. event-related fMRI**
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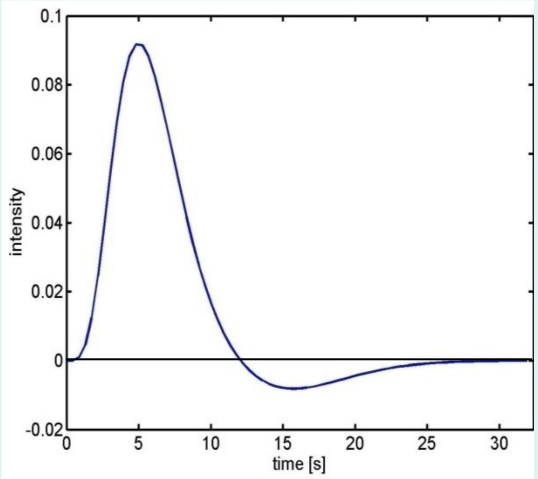
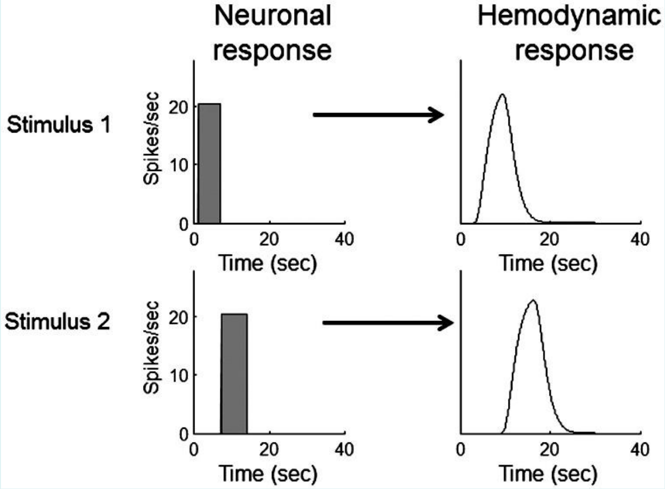
# BOLD response

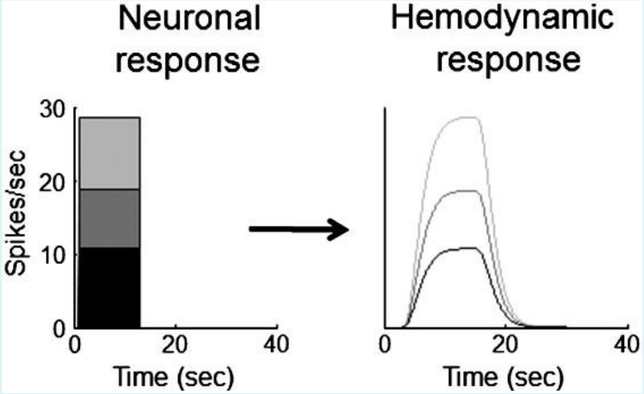
Hemodynamic response function (HRF):



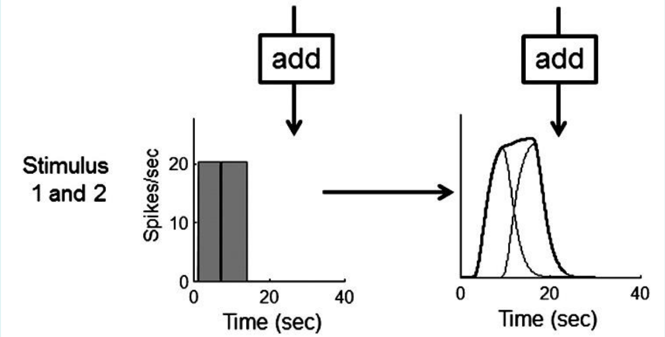

Shift invariance




Scaling



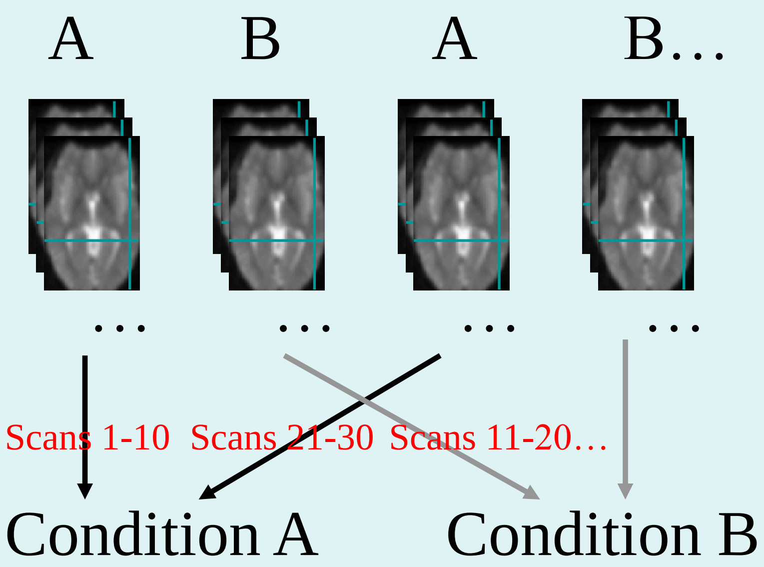

Additivity

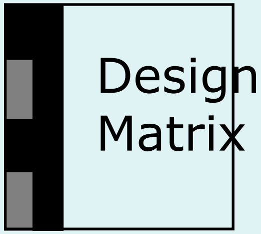



Boynton et al, NeuroImage, 2012.

# Epoch vs. event related design

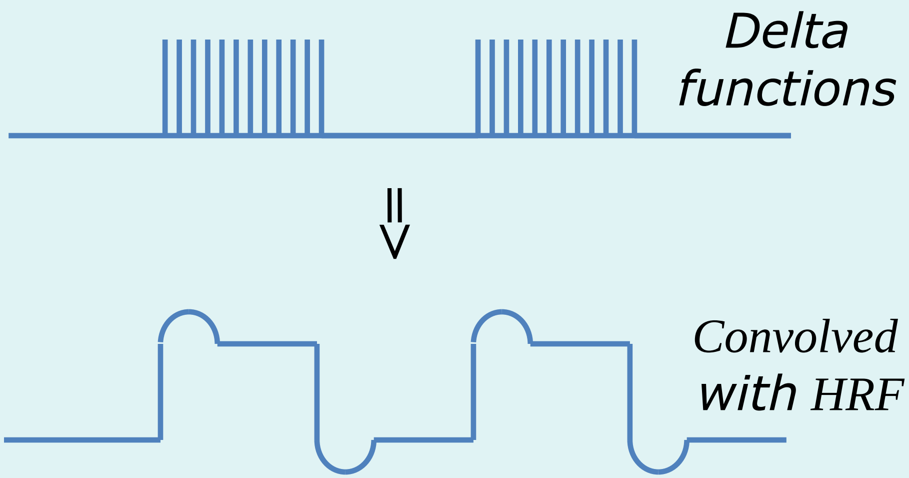
"PET Blocked conception"
*(scans assigned to conditions)*




"fMRI Epoch conception"
*(scans treated as timeseries)*


"fMRI Event-related conception"



# Advantages of Event-Related design

- Randomised trial order

  *c.f. confounds of blocked designs*

Blocked designs may trigger expectations and cognitive sets


Intermixed designs can minimise this by stimulus randomisation

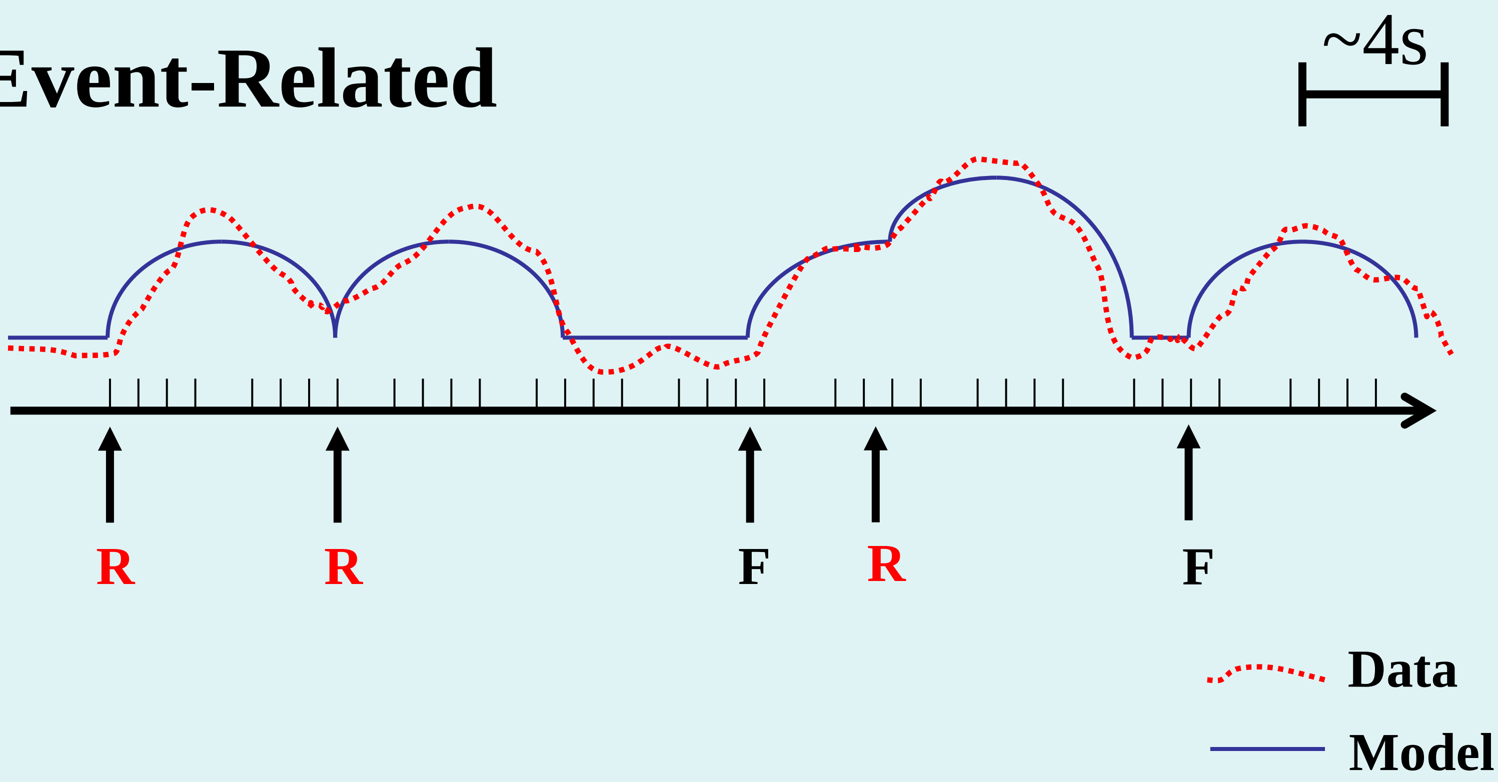
# Advantages of Event-Related design

- Randomised trial order
  *c.f. confounds of blocked designs*
- Post hoc / subjective classification of trials
  *e.g, according to subsequent memory*

**R** = **Words Later Remembered**

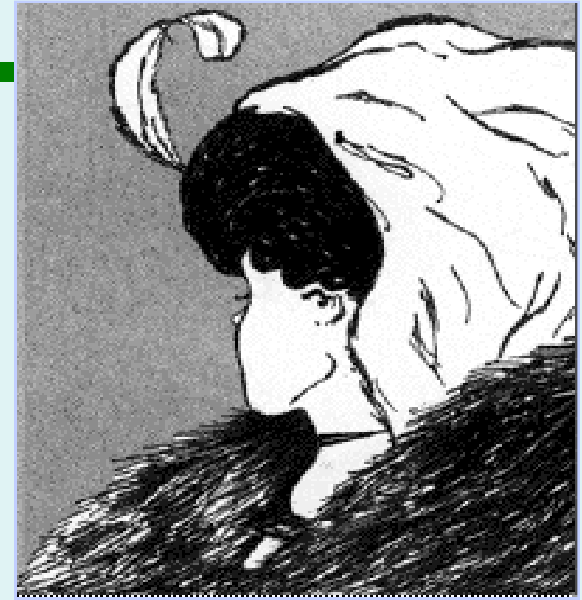
**F = Words Later Forgotten**

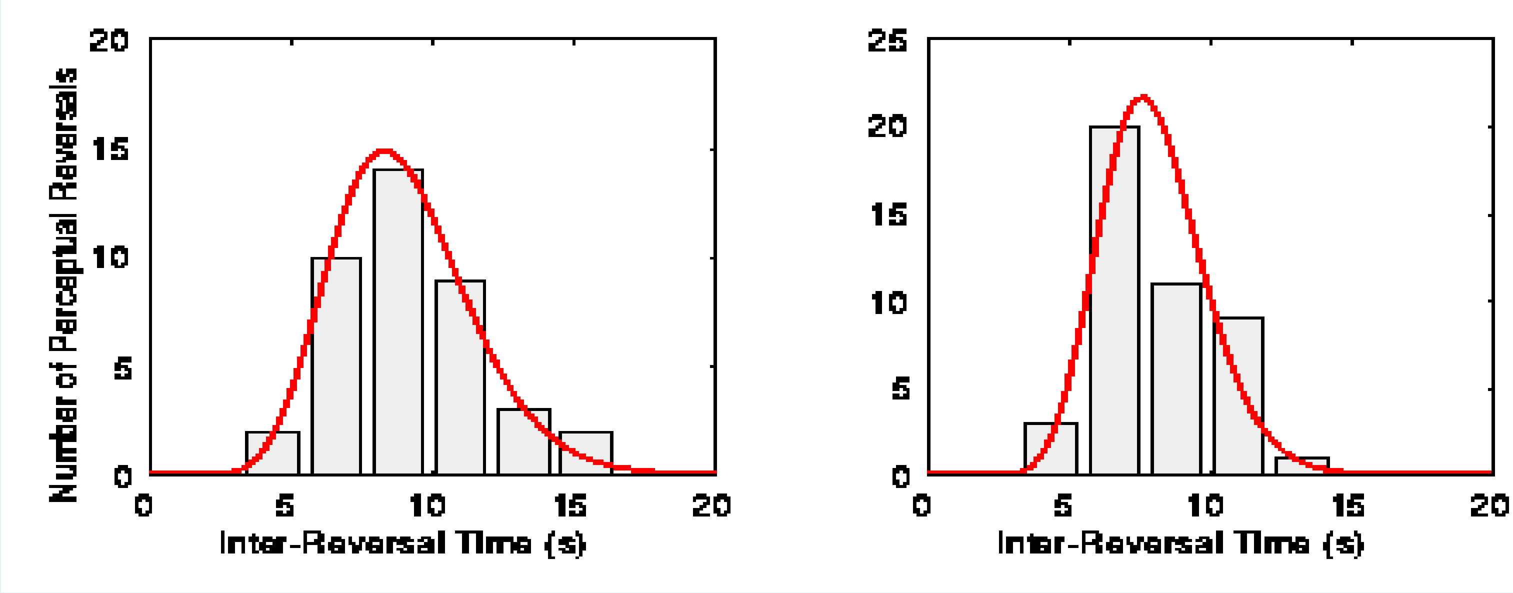
# Event-Related



# Advantages of Event-Related design

- Randomised trial order
  *c.f. confounds of blocked designs*
- Post hoc / subjective classification of trials
  *e.g, according to subsequent memory*
- Some events can only be indicated (in time)
  *e.g, spontaneous perceptual changes*




Number of Perceptual Reversals
Inter-Reversal Time (s)
Inter-Reversal Time (s)

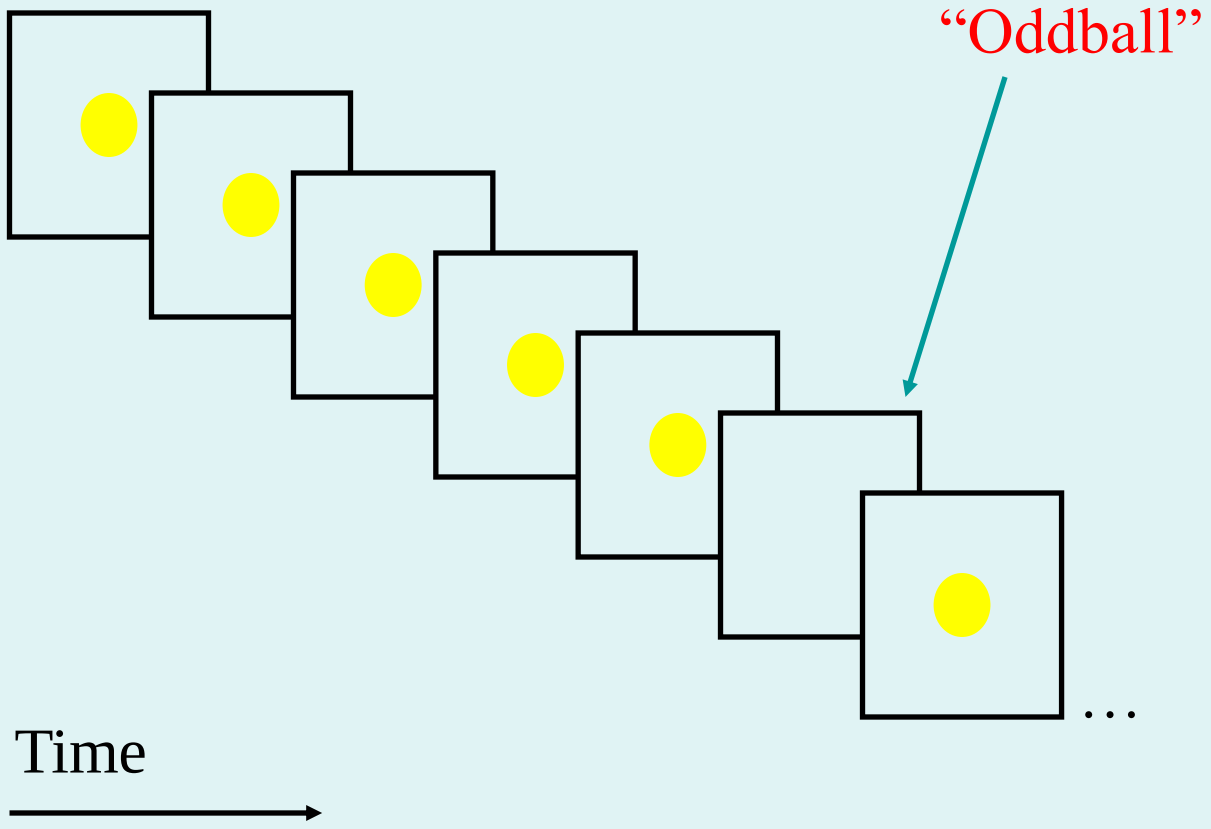
# Advantages of Event-Related design

- Randomised trial order
  *c.f. confounds of blocked designs*

- Post hoc / subjective classification of trials
  *e.g, according to subsequent memory*

- Some events can only be indicated (in time)
  *e.g, spontaneous perceptual changes*

- Some trials cannot be blocked
  *e.g, "oddball" designs*


"Oddball"
. . .
Time

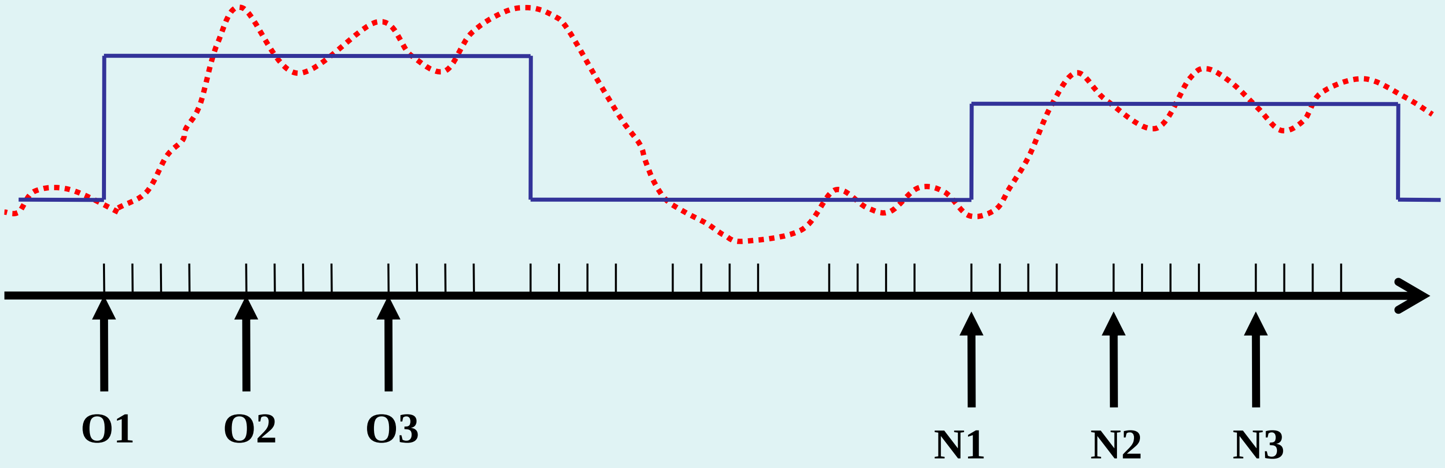
# Advantages of Event-Related design

- Randomised trial order
  *c.f. confounds of blocked designs*
- Post hoc / subjective classification of trials
  *e.g, according to subsequent memory*
- Some events can only be indicated (in time)
  *e.g, spontaneous perceptual changes*
- Some trials cannot be blocked
  *e.g, "oddball" designs*
- More accurate models even for blocked designs?
  *e.g, "state-item" interactions*

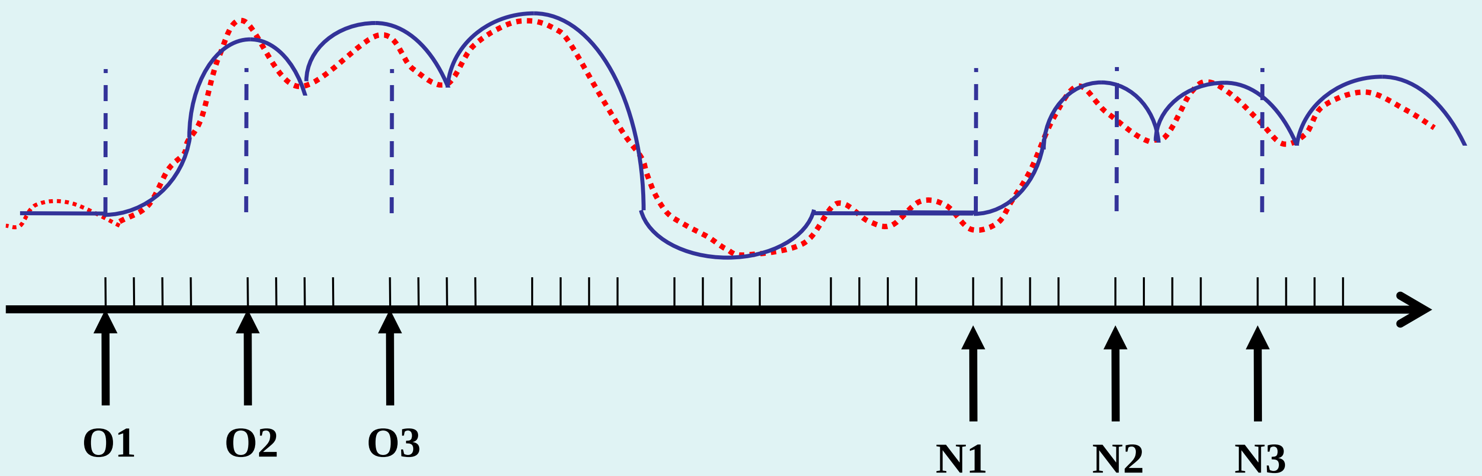
# Blocked Design

Data
Model

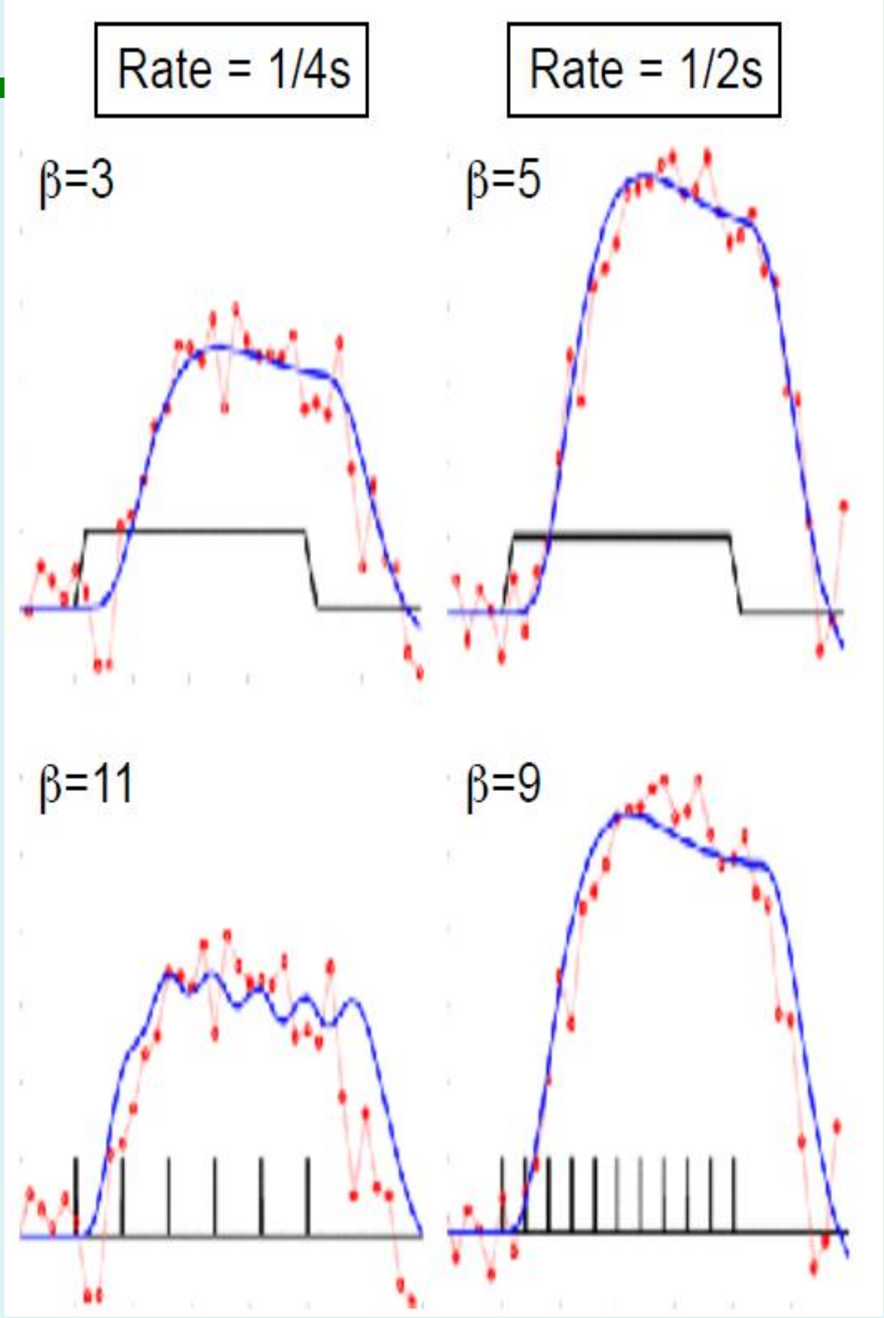
## “Epoch” model




## “Event” model



- Blocks of trials can be modeled as boxcars or runs of events
- BUT: interpretation of the parameter estimates may differ
- Consider an experiment presenting words at different rates in different blocks:
  - An “epoch” model will estimate parameter **that increases with rate**, because the parameter reflects response per block
  - An “event” model may estimate parameter **that decreases with rate**, because the parameter reflects response per word



# Disadvantages of ER designs

- Less efficient for detecting effects than are blocked designs *(see later…)*
- Some psychological processes may be better blocked (e.g. task-switching, attentional instructions)

# Content

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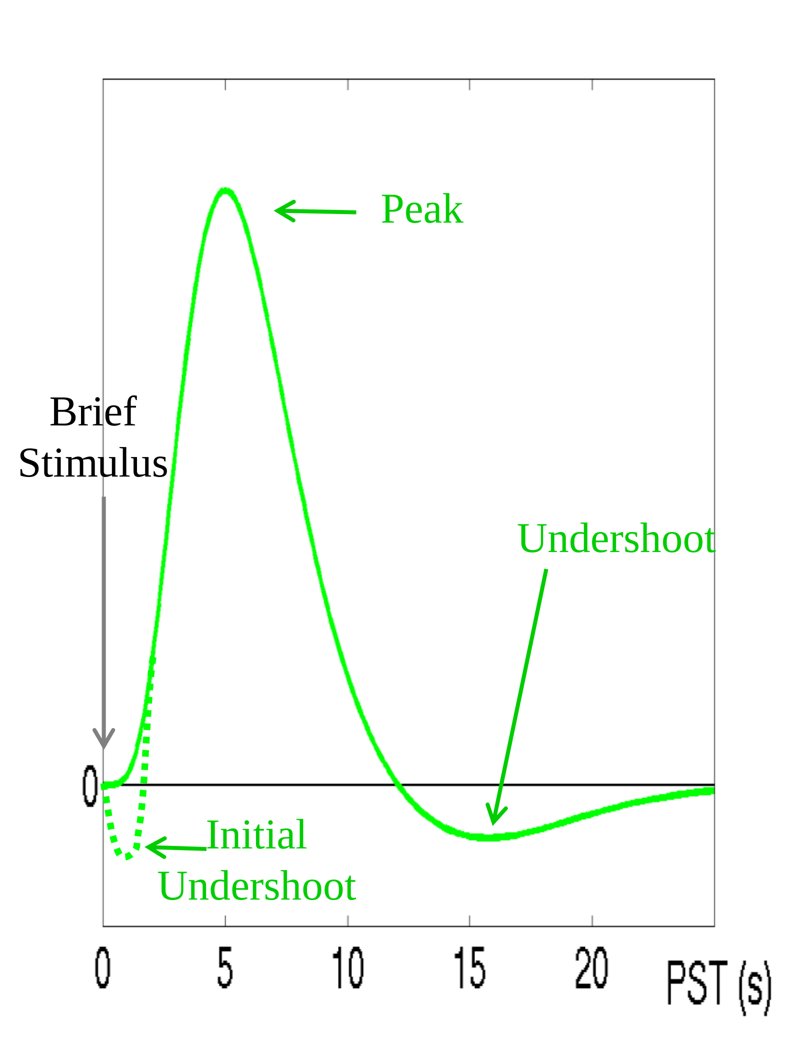
- (Dis)Advantages of efMRI
- **GLM: Convolution**
- **BOLD impulse response**
- Temporal Basis Functions
- Timing Issues
- Design Optimisation – “Efficiency”

# Haemodynamic response function

- 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) and individuals (Aguirre et al, 1998)



# General Linear (Convolution) Model

GLM for a single voxel:

$$y(t) = u(t) \otimes h(\tau) + \varepsilon(t)$$

$u(t)$ = neural causes (stimulus train)

$$u(t) = \sum \delta\,(t - nT)$$

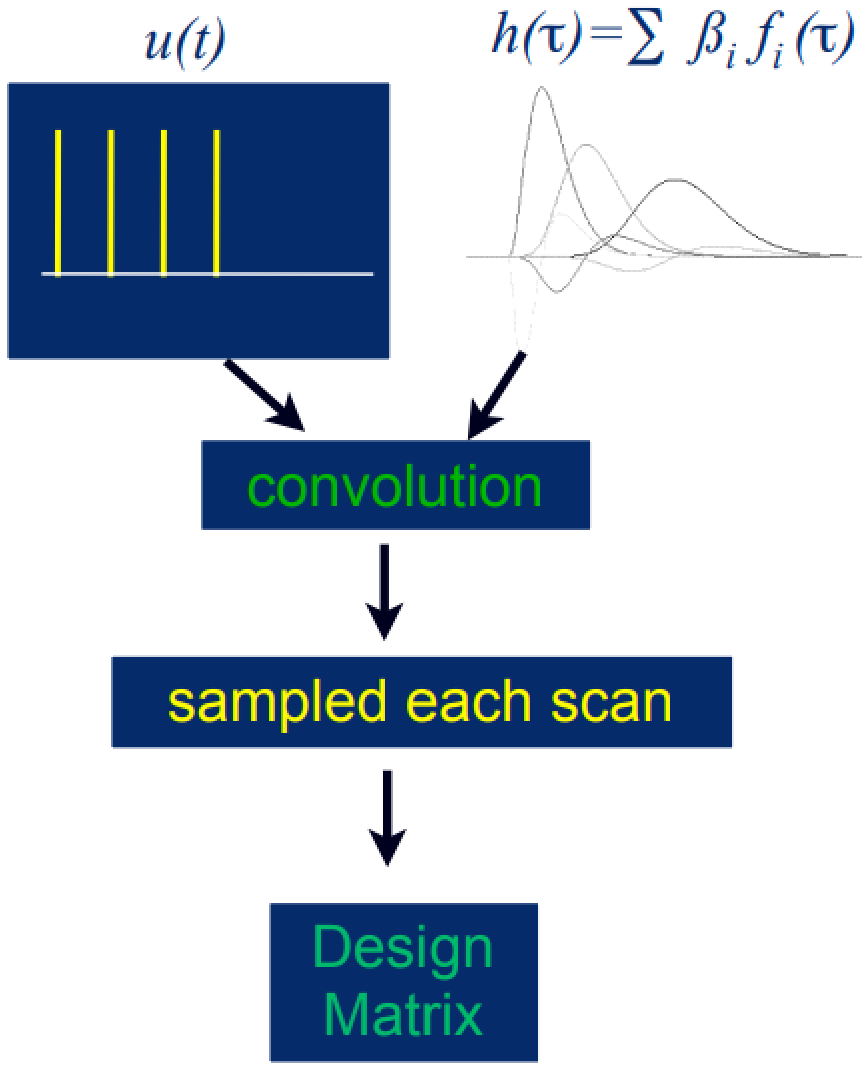
$h(\tau)$ = hemodynamic (BOLD) response

$$h(\tau) = \sum \beta_i\, f_i(\tau)$$

$f_i(\tau)$ = temporal basis functions

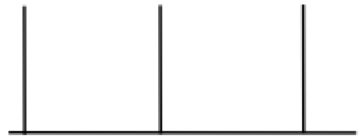
$$y(t) = \sum \sum \beta_i\, f_i(t - nT) + \varepsilon(t)$$

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$$

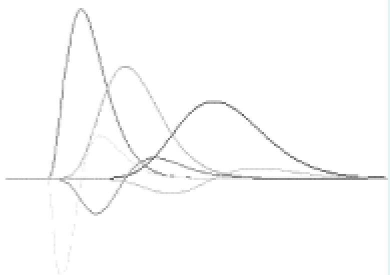


# General Linear Model in SPM

Stimulus every 20s



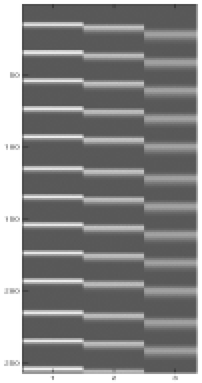
Gamma functions $f_i(\tau)$ of peristimulus time $\tau$ (Orthogonalised)



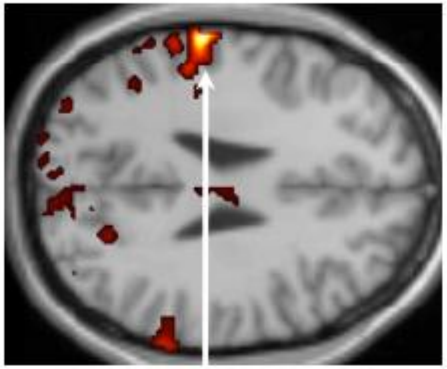
Sampled every TR = 1.7s

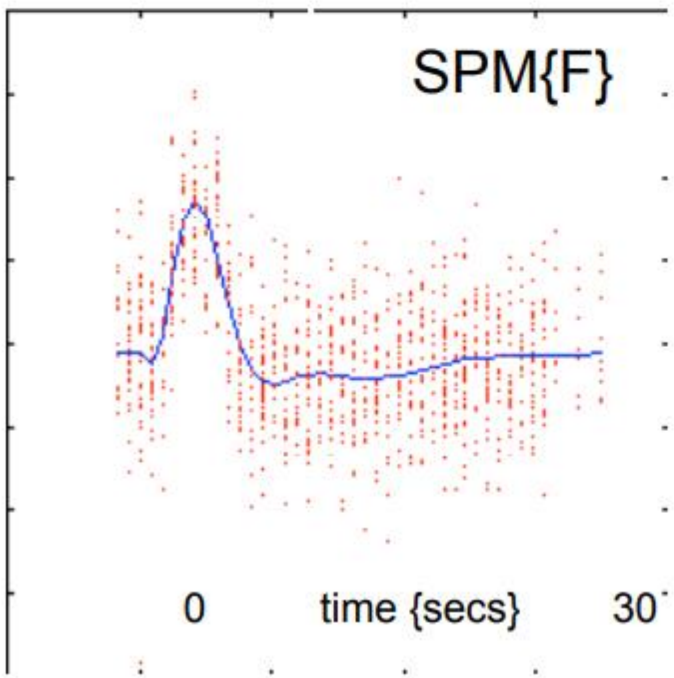
Design matrix, $\mathbf{X}$

$[x(t) \otimes f_1(\tau) \mid x(t) \otimes f_2(\tau) \mid \ldots]$



…





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- **Temporal Basis Functions**
- Timing Issues
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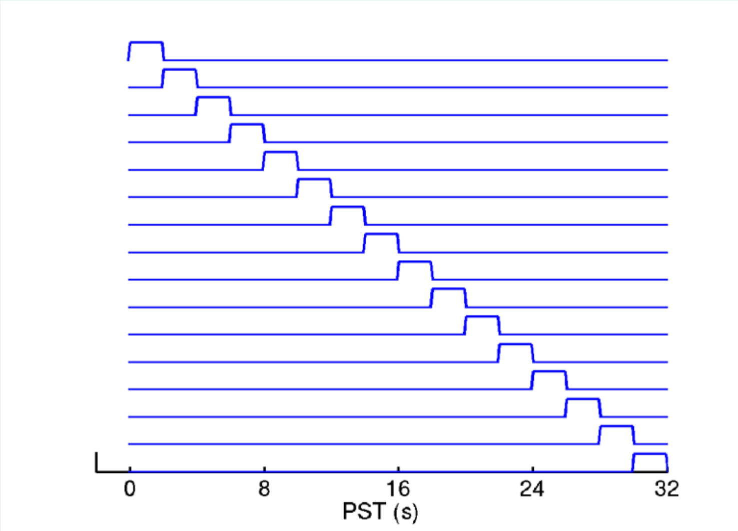
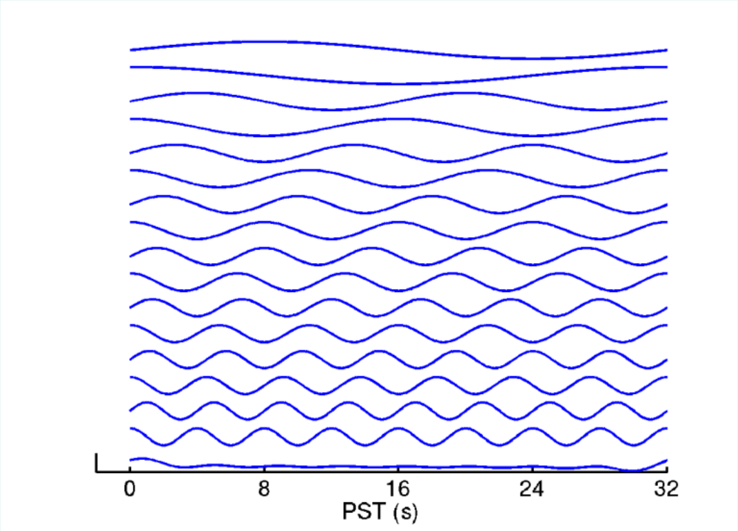
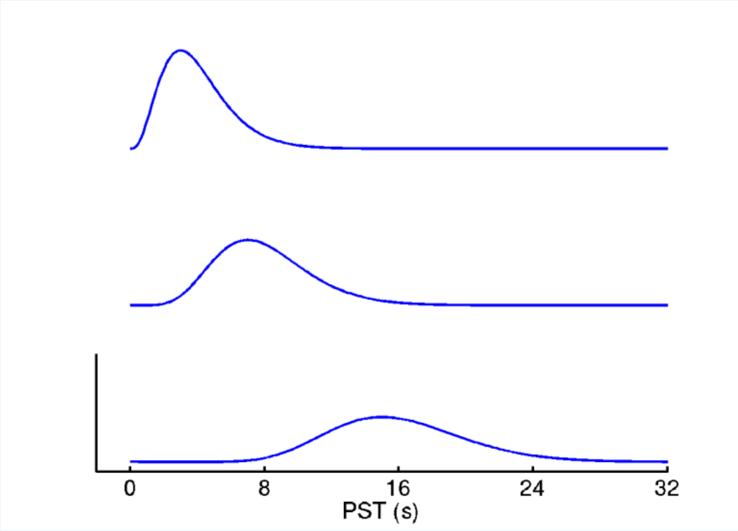
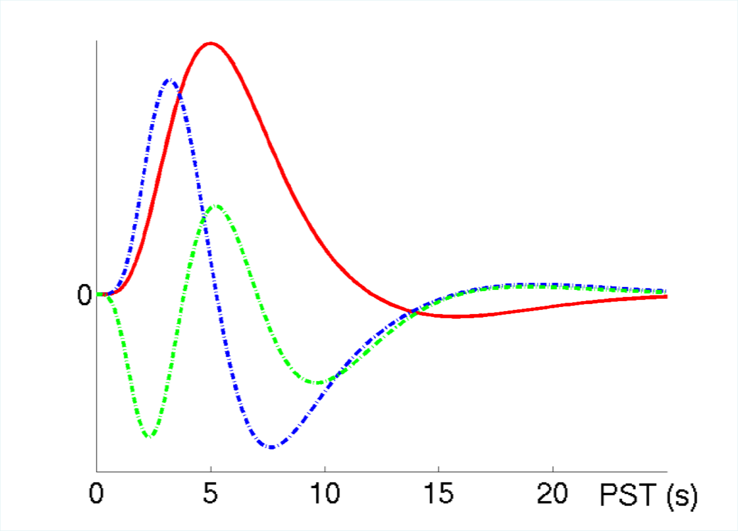
# Temporal Basis Functions



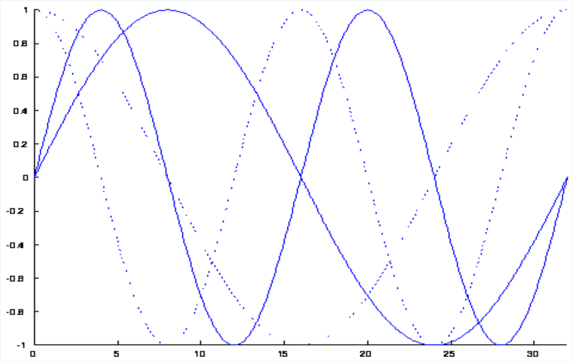



# Temporal Basis Functions

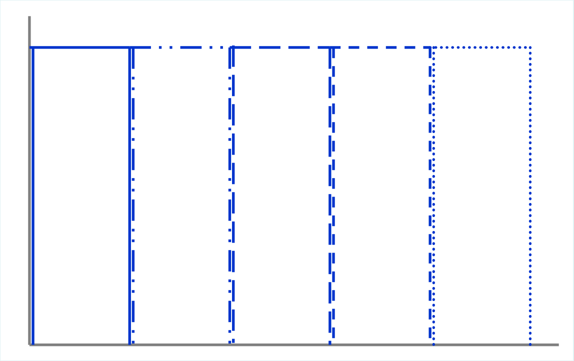
- Fourier Set

  Windowed sines & cosines
  Any shape (up to frequency limit)
  Inference via F-test




- Finite Impulse Response (FIR)

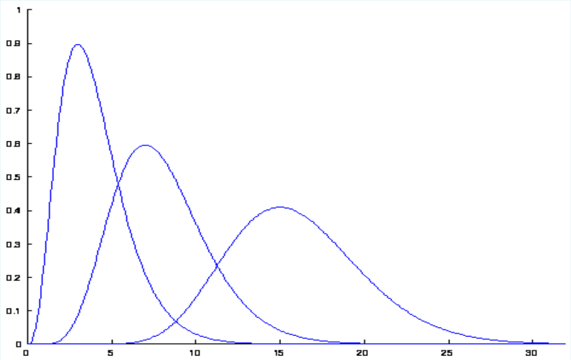
  Mini timebins (selective averaging)
  Any shape (up to bin-width)
  Inference via F-test



# Temporal Basis Functions

- Gamma Functions

  Bounded, asymmetrical (like BOLD)
  Set of different lags
  Inference via F-test



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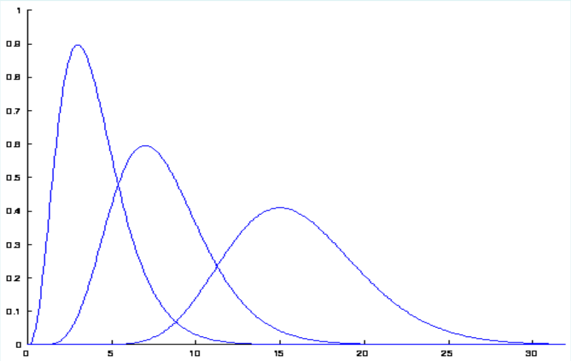
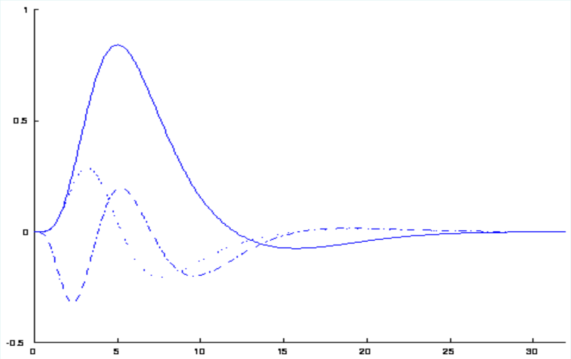
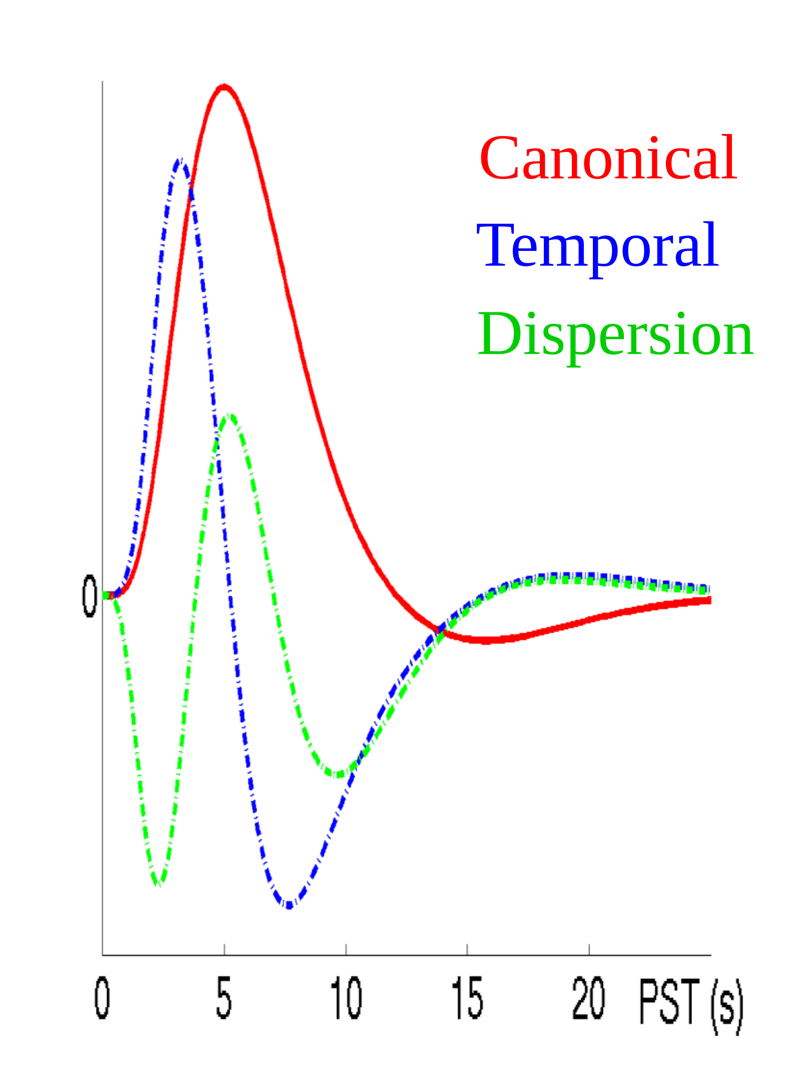



- Informed Basis Set

  Best guess of canonical BOLD response
  Variability captured by Taylor expansion
  “Magnitude” inferences via t-test…?



# Temporal Basis Functions




- Informed Basis Set

  *(Friston et al. 1998)*

- Canonical HRF (2 gamma functions)

  *plus* Multivariate Taylor expansion in:

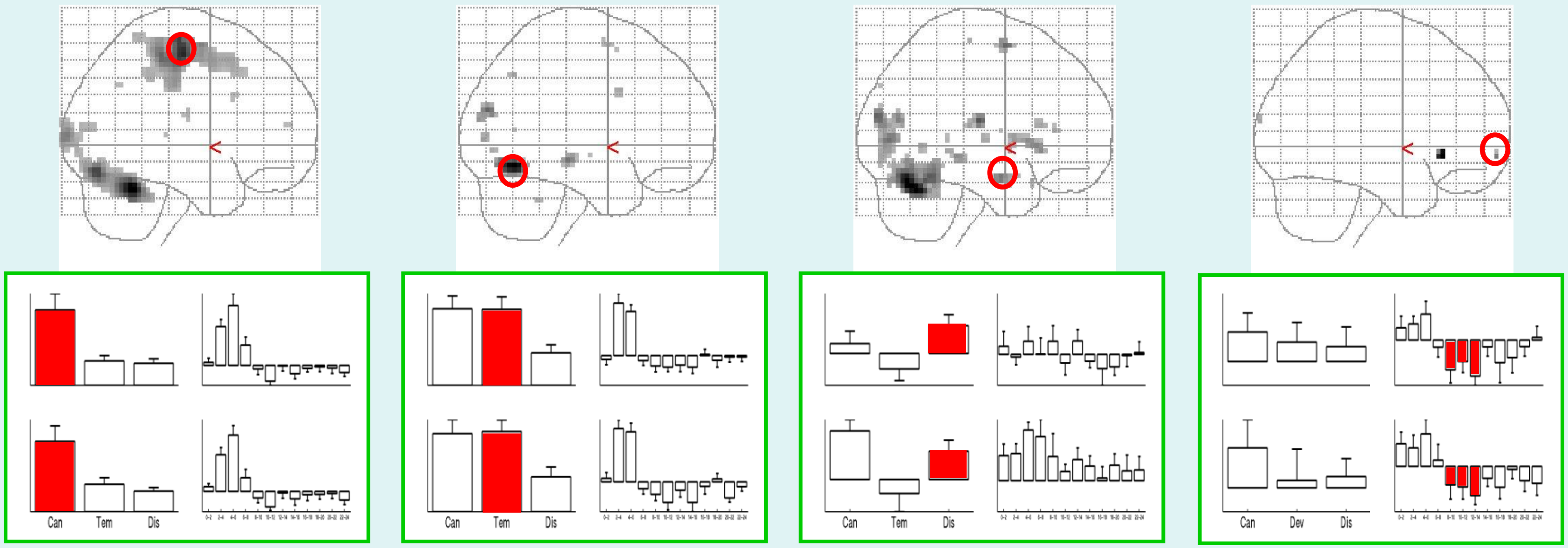
  time (*Temporal Derivative*)

  width *(Dispersion Derivative)*

- "Magnitude" inferences via t-test on canonical parameters (providing canonical is a good fit…more later)
- "Latency" inferences via tests on *ratio* of derivative : canonical parameters (more later…)

# Temporal Basis Functions, which one(s)?

In this example (rapid motor response to faces, *Henson et al, 2001*)…




Canonical + Temporal + Dispersion + FIR

…canonical + temporal + dispersion derivatives appear sufficient

…may not be for more complex trials (eg stimulus-delay-response)

…but then such trials better modelled with separate neural components (ie activity no longer delta function) + constrained HRF (Zarahn, 1999)

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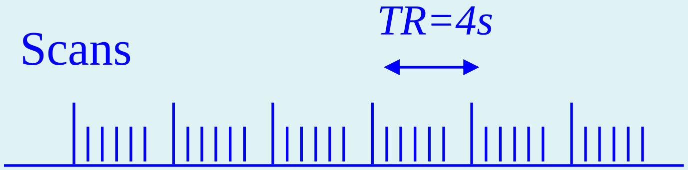
# Timing Issues

- Typical TR for 48 slice EPI at 3mm spacing is ~ 4s



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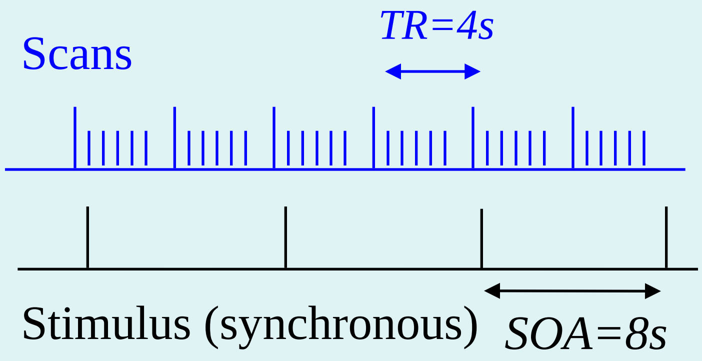
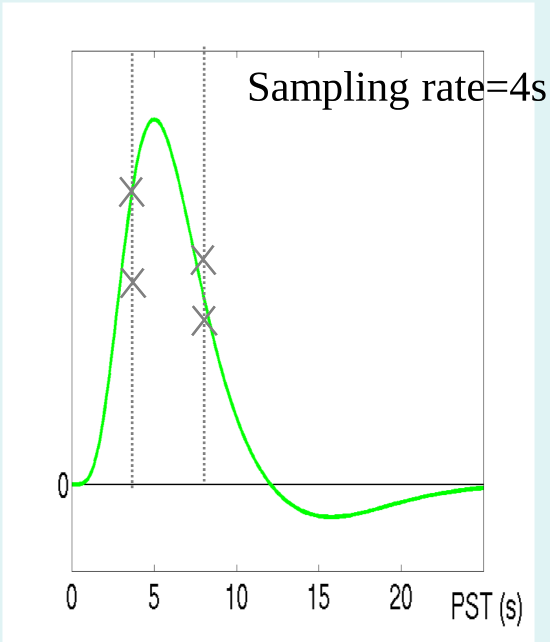
- Sampling at [0,4,8,12…] post- stimulus may miss peak signal



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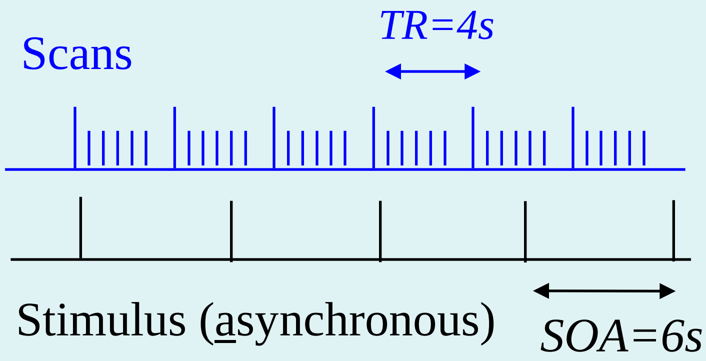
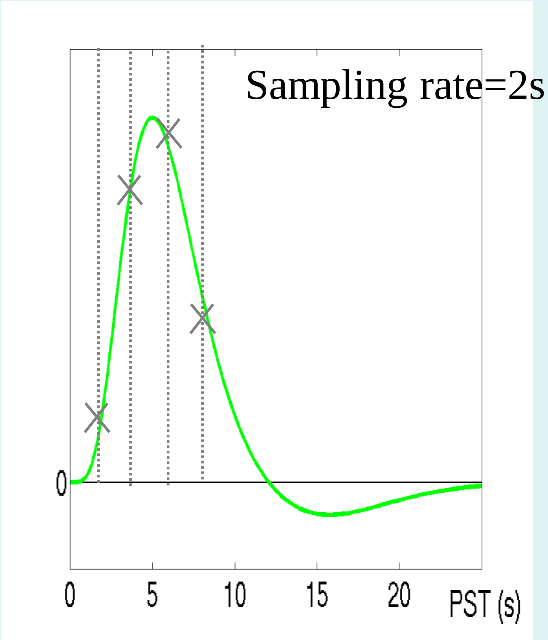
- Higher effective sampling by:
    1. Asynchrony, *e.g. SOA=1.5TR*



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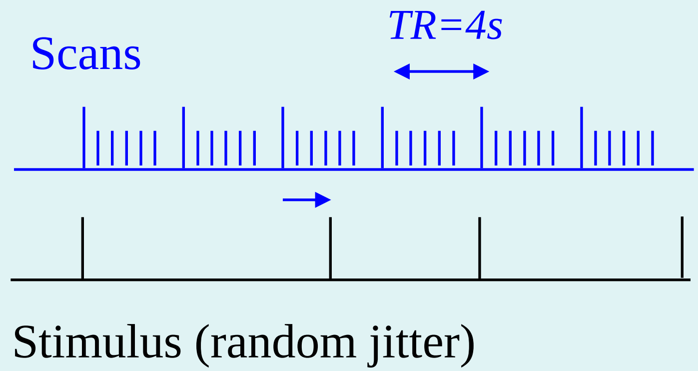
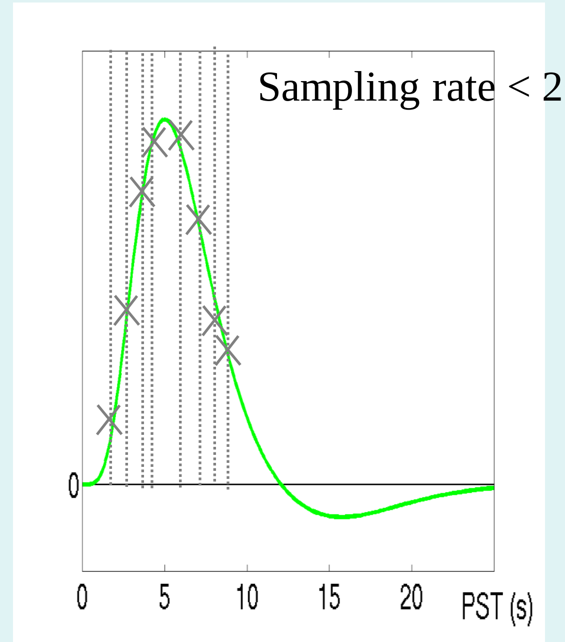
- Typical TR for 48 slice EPI at 3mm spacing is ~ 4s
- Sampling at [0,4,8,12…] post- stimulus may miss peak signal
- Higher effective sampling by:

  1. Asynchrony, *e.g.* *SOA=1.5TR*
  2. Random Jitter, e.g. *SOA=(2±0.5)TR*



# BOLD Response Latency (Linear)

- Assume the real response, $r(t)$, is a scaled (by $\alpha$) version of the canonical, $f(t)$, but delayed by a small amount $dt$:

$$r(t) = \alpha f(t+dt) \sim \alpha f(t) + \alpha f'(t)\, dt \qquad \textit{1}^{st}\textit{-order Taylor}$$

- If the fitted response, $R(t)$, is modelled by the canonical + temporal derivative:

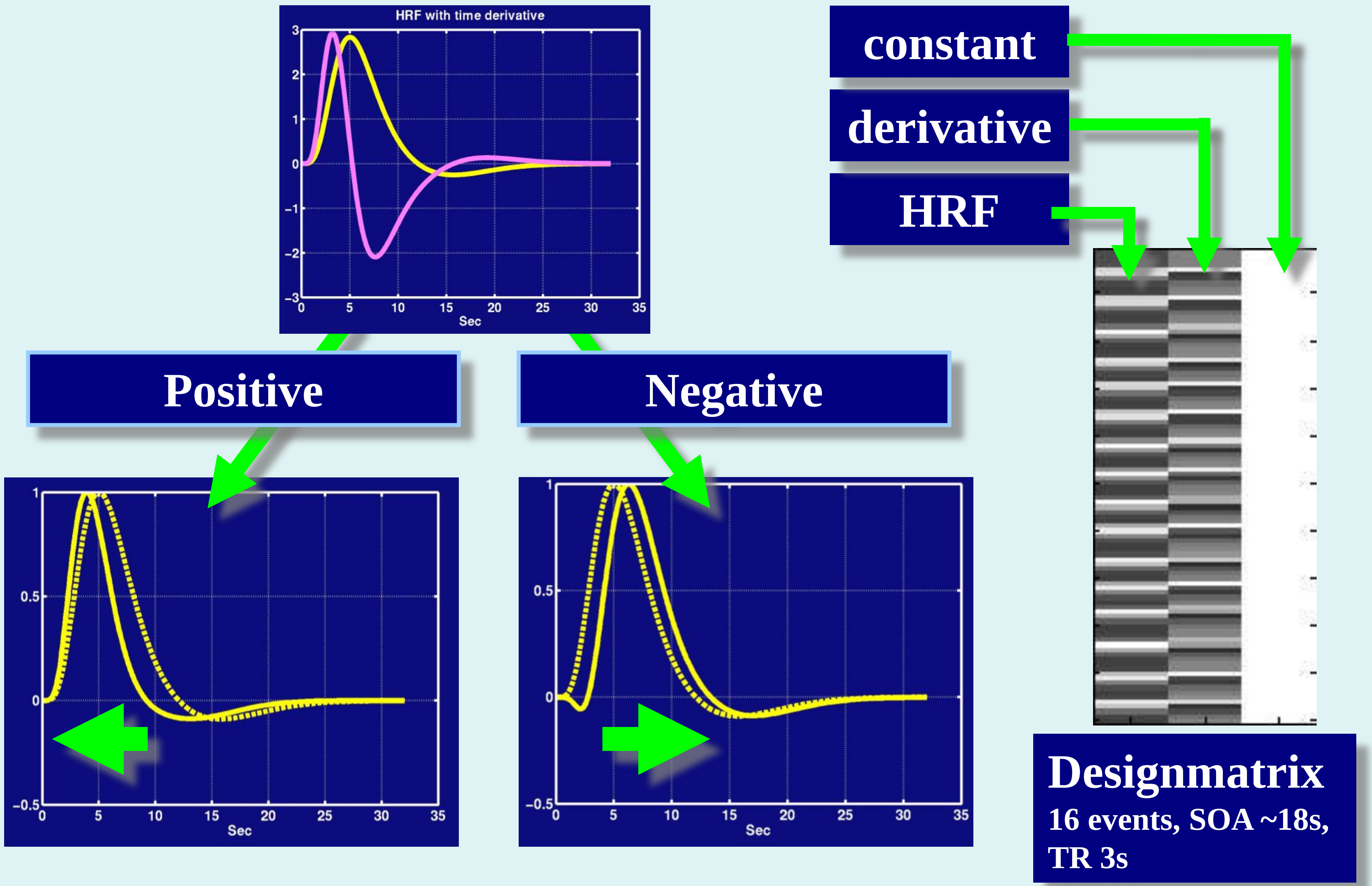
$$R(t) = ß_1 f(t) + ß_2 f'(t) \qquad \textit{GLM fit}$$

- Then canonical and derivative parameter estimates, $ß_1$ and $ß_2$, are such that:

$$\alpha = ß_1 , \quad dt = ß_2 / ß_1$$

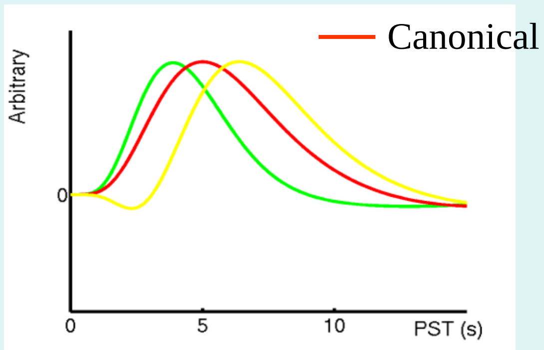
- *i.e. latency can be approximated by the ratio of derivative-to-canonical parameter estimates (within limits of first-order approximation, +/- 1s)*

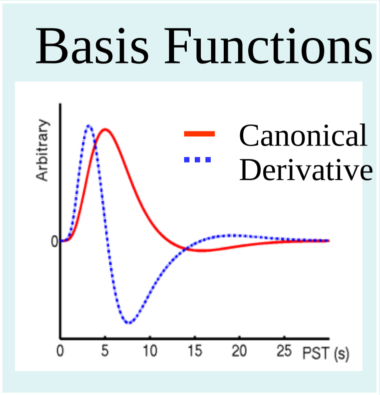
# BOLD Response Latency: example

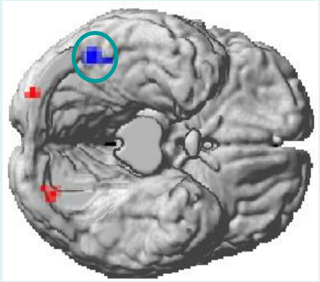


# BOLD Response Latency (Linear)

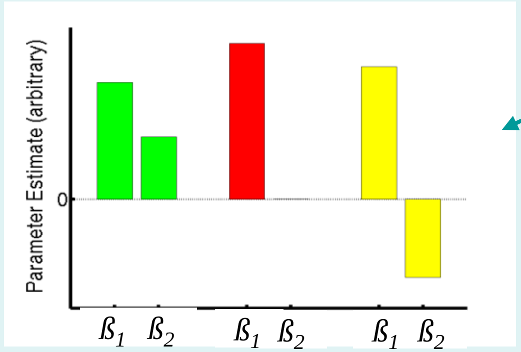
Delayed Responses
(green/yellow)

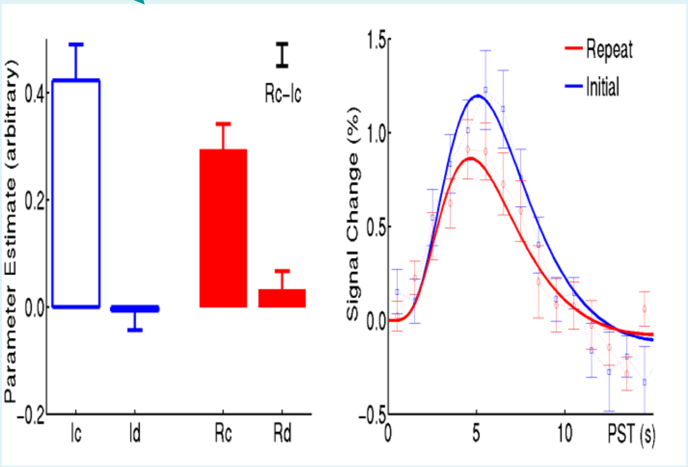


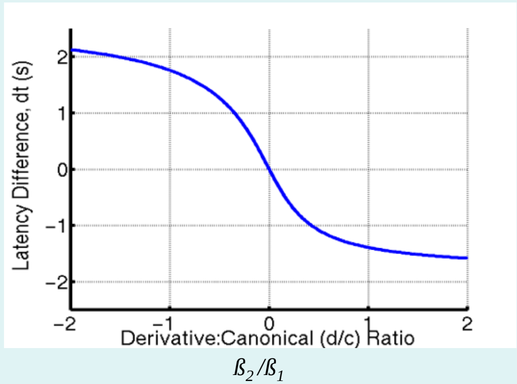



Parameter Estimates




Actual latency, $dt$, vs. $ß_2 / ß_1$




*Face repetition reduces latency as well as magnitude of fusiform response*

# Neural Response Latency

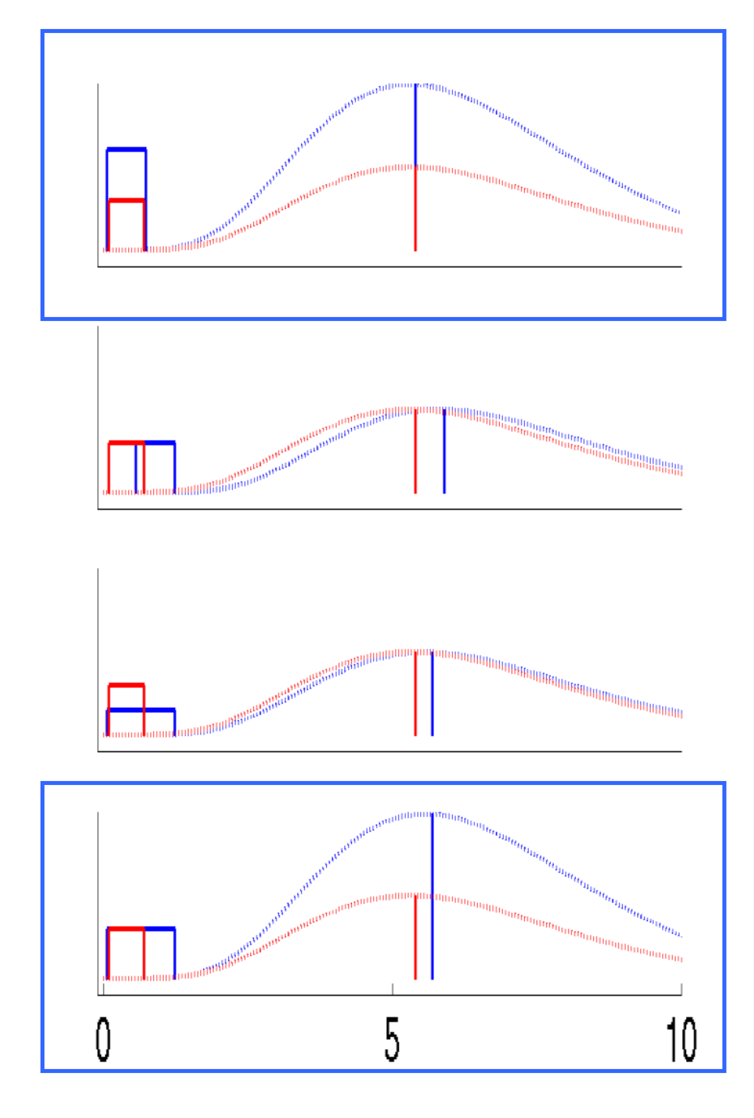
*Neural*

A. Decreased

B. Advanced

C. Shortened (same integrated)

D. Shortened (same maximum)




*BOLD*

A. Smaller Peak

B. Earlier Onset

C. Earlier Peak

D. Smaller Peak *and earlier Peak*

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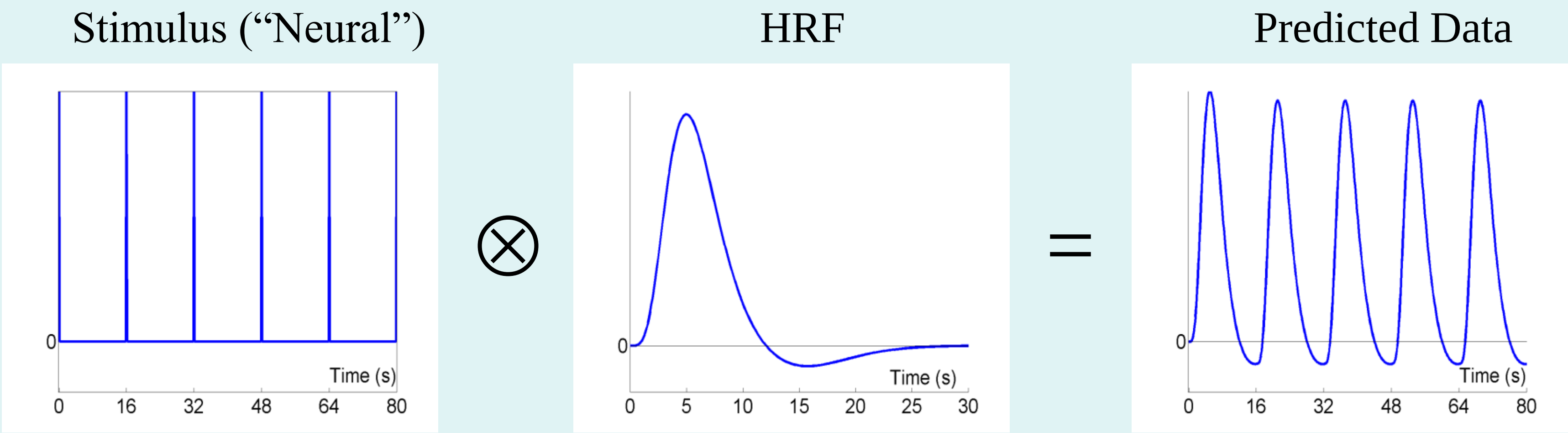
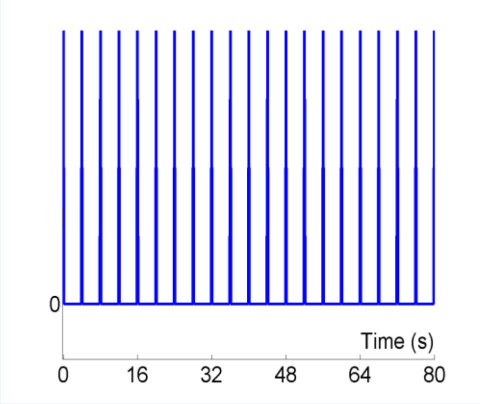
# Fixed SOA = 16s




*Not particularly efficient…*

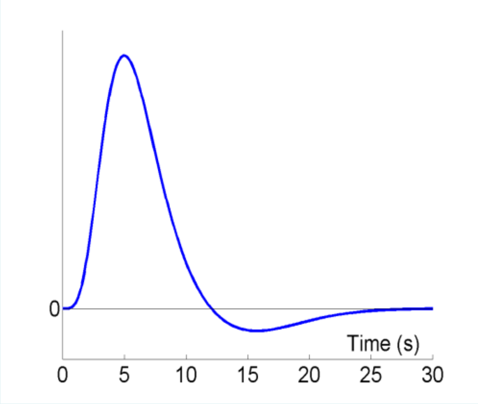
# Fixed SOA = 4s

Stimulus ("Neural")




⊗

HRF

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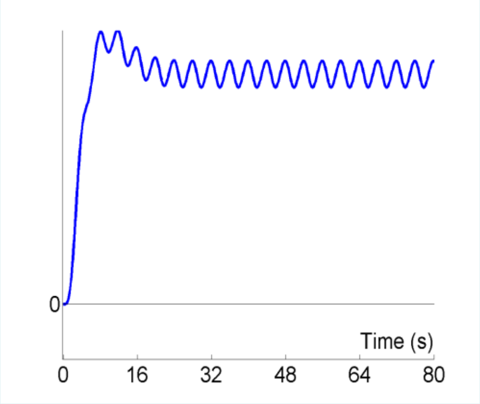
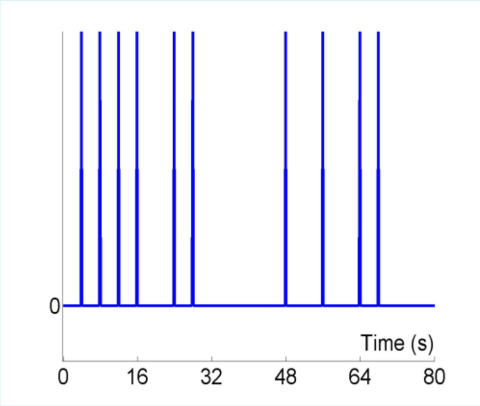
Predicted Data




*Very Inefficient…*

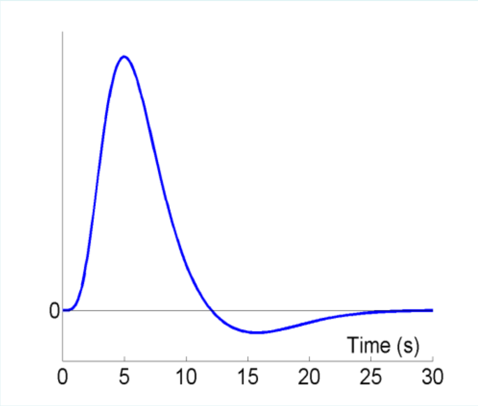
# Randomised, $SOA_{min}$= 4s

Stimulus (“Neural”)




$\otimes$

HRF

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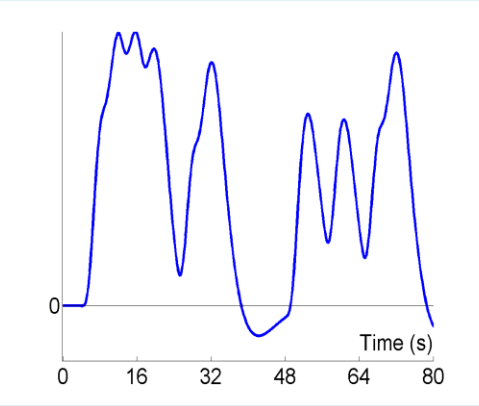
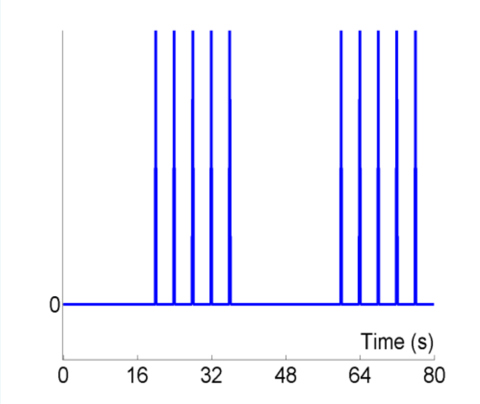
Predicted Data




*More Efficient…*

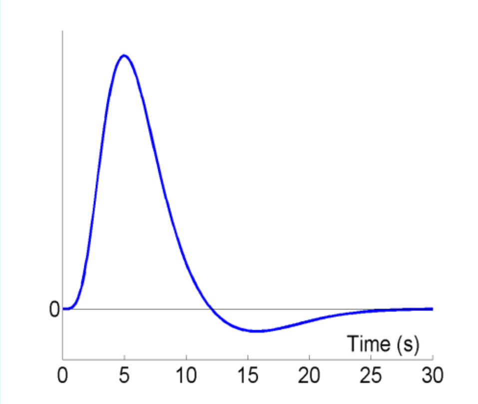
# Blocked, $SOA_{min}$ = 4s

Stimulus ("Neural")



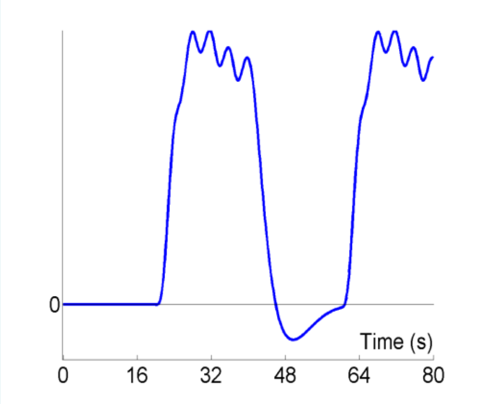

⊗

HRF




=

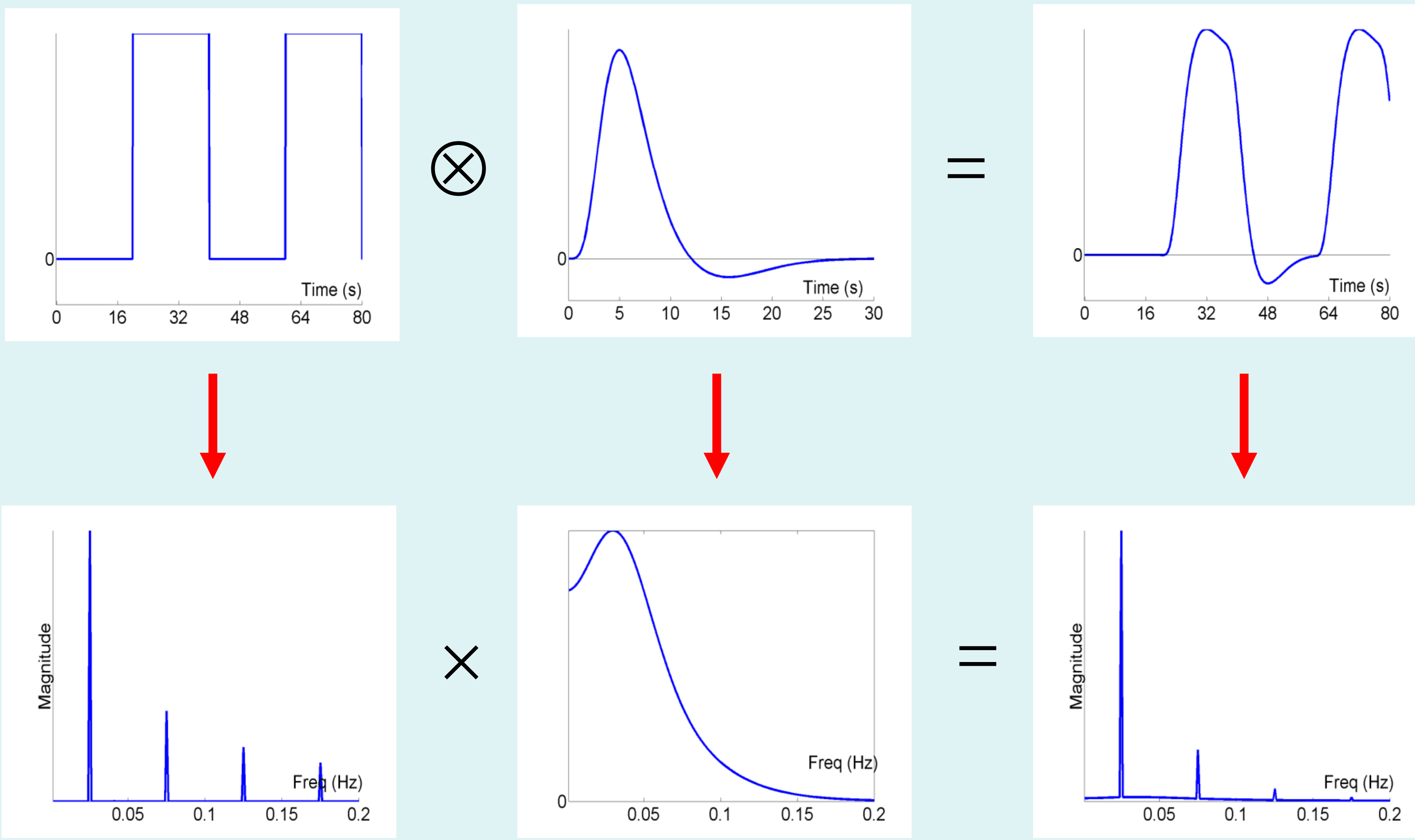
Predicted Data




*Even more Efficient…*

# Blocked, epoch = 20s

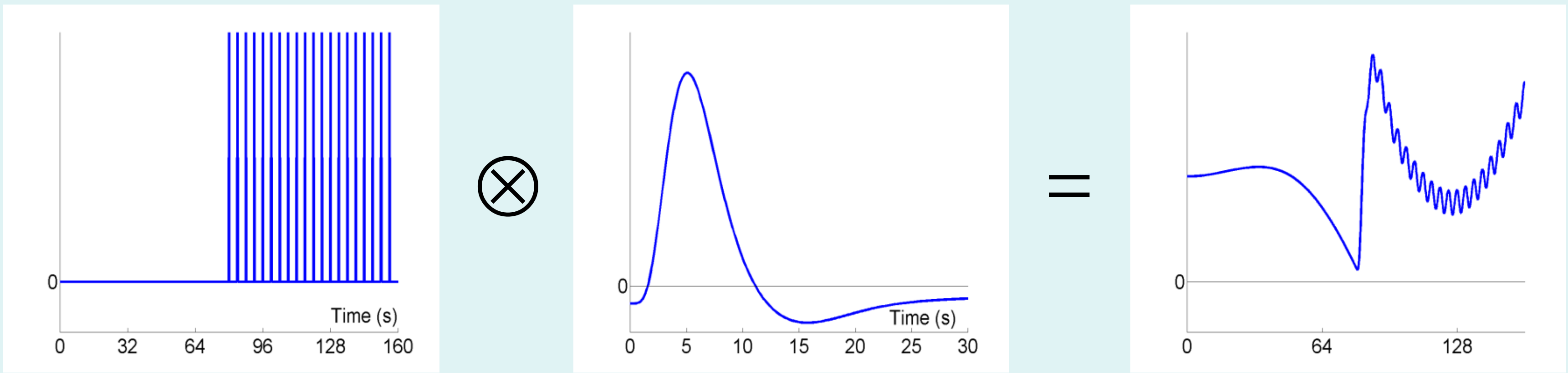
Stimulus ("Neural") HRF Predicted Data



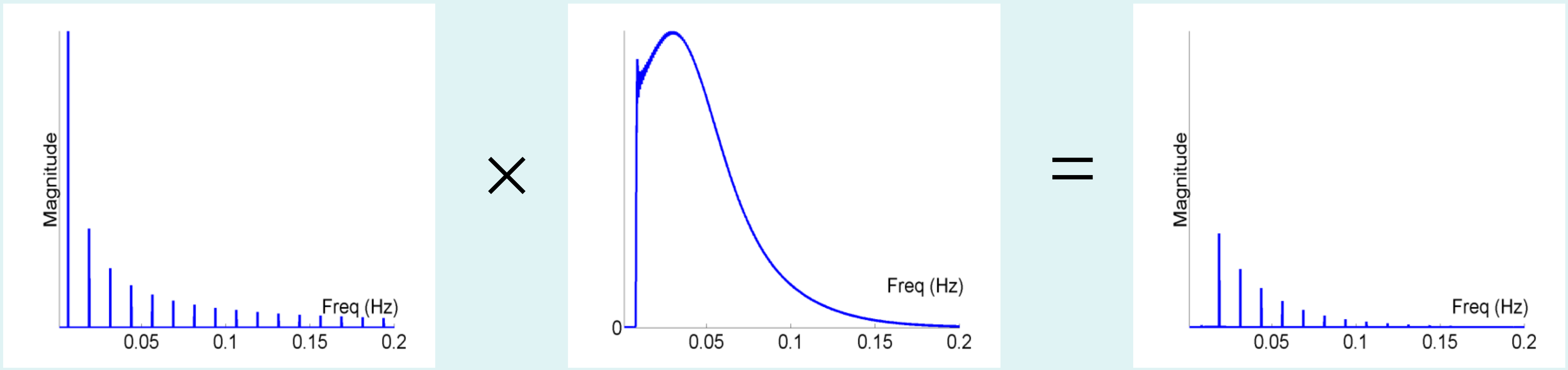

*Blocked-epoch (with small SOA) and Time-Freq equivalences*

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

Stimulus ("Neural") HRF Predicted Data



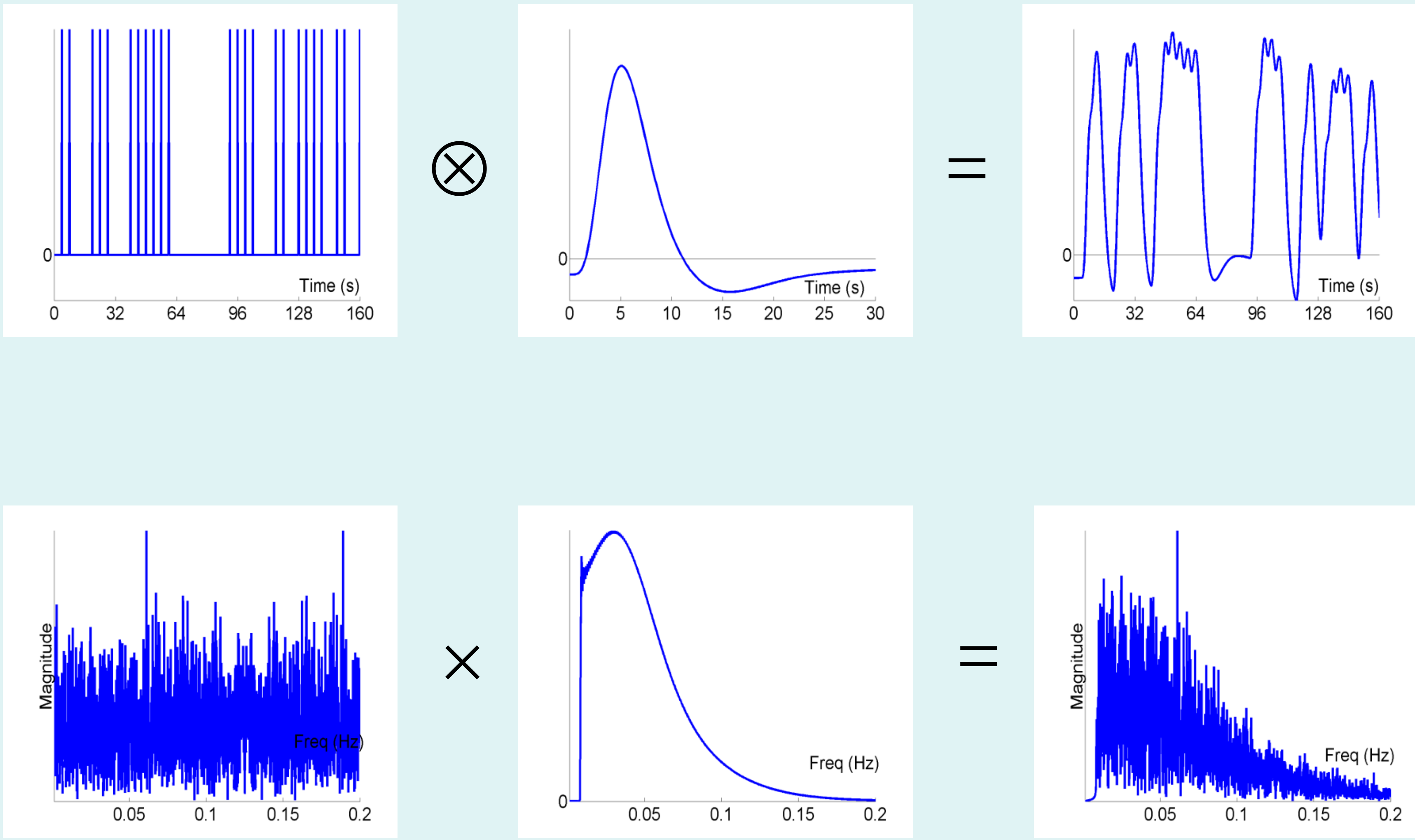

"Effective HRF" (after highpass filtering)
(Josephs & Henson, 1999)




*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)*

# Design Efficiency

Maximise efficiency by maximising t, by minimising the squared variance:

$$t = \frac{c^T \beta}{\sqrt{\mathrm{var}(c^T \beta)}}$$

X: design matrix
c: contrast vector
β: beta vector

Assuming that the error in our model is 'iid', each observation is drawn independently from a Gaussian distribution:

$$b \sim N(b, s^2 (X^T X)^{-1})$$

$$\mathrm{var}(c^T b) = s^2 c^T (X^T X)^{-1} c$$

Assuming σ is independent of our design, taking a fixed contrast we can only alter our design matrix to improve efficiency.

Formal definition of **design efficiency** minimises variance:

$$e \gg \frac{1}{\sqrt{c^T (X^T X)^{-1} c}}$$

Given the contrast of interest, **minimise covariance in the design matrix**

***Efficiency can be estimated before using the design***

# Design efficiency: Trial sequencing

- Design parametrised by:

  $SOA_{min}$ Minimum SOA

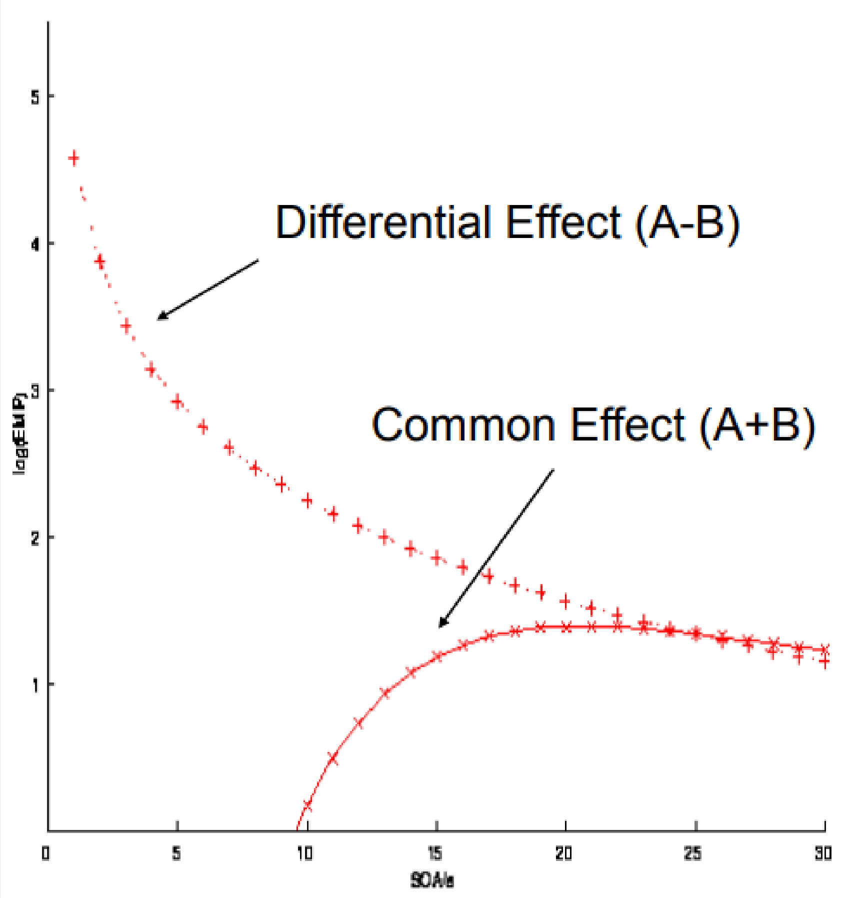
  $p_i(\mathbf{h})$ Probability of event-type *i* given history ***h*** of last *m* events

- With *n* event-types $p_i(\mathbf{h})$ is a *n x n Transition Matrix*

- Example: Randomised AB

| | A | B |
|---|---|---|
| **A** | 0.5 | 0.5 |
| **B** | 0.5 | 0.5 |

**=> ABBBABAABABAAA...**



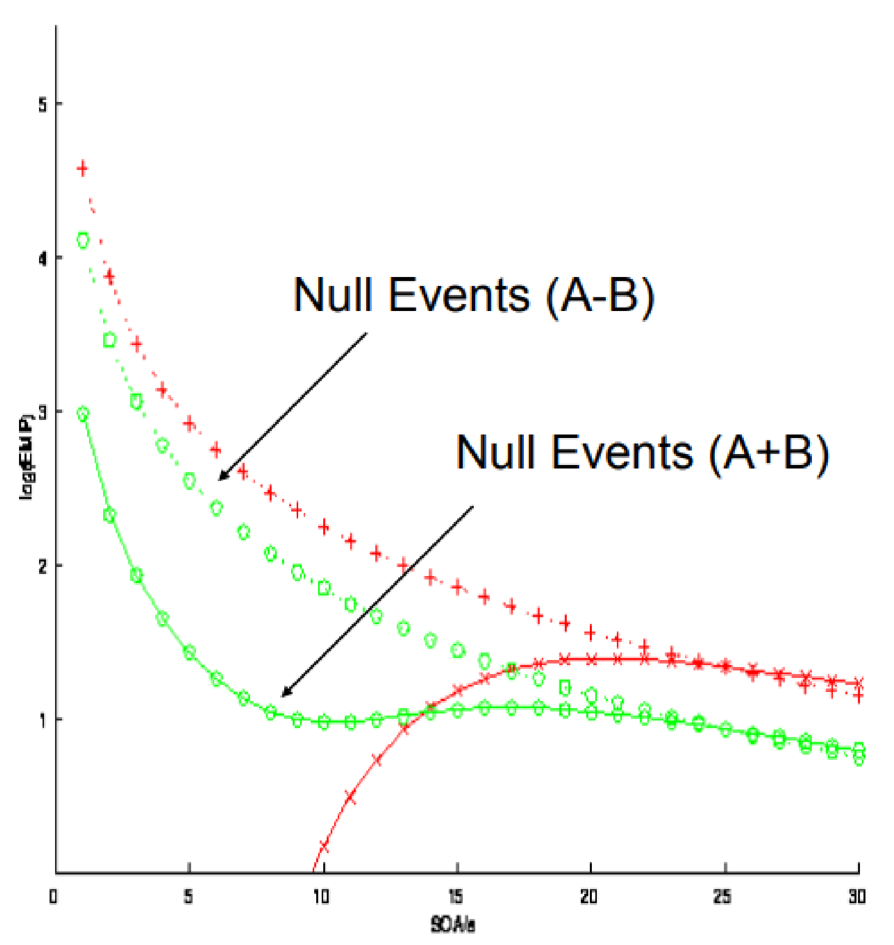
# Design efficiency: Trial sequencing

- 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)



# Design efficiency: Trial sequencing

- Example: Alternating AB

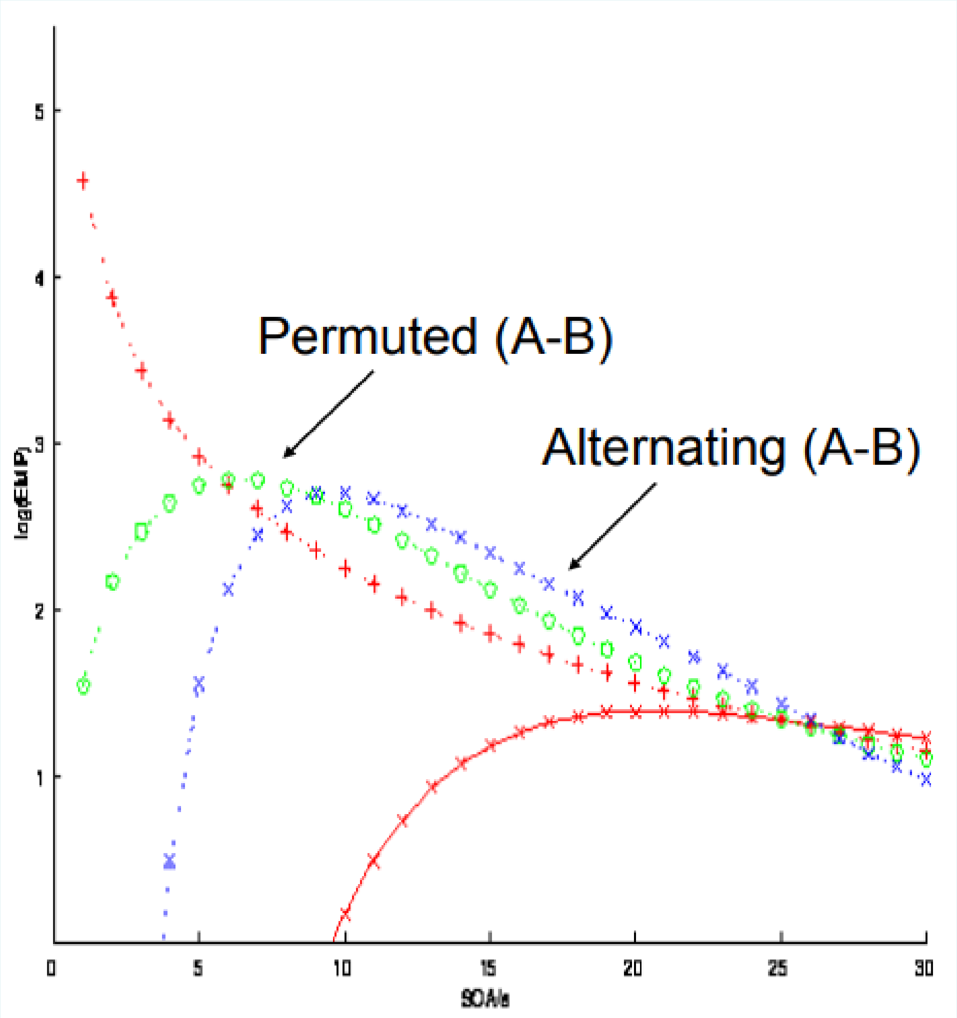
| | A | B |
|---|---|---|
| A | 0 | 1 |
| B | 1 | 0 |

=> **ABABABABABAB...**

- Example: Permuted AB

| | A | B |
|---|---|---|
| AA | 0 | 1 |
| AB | 0.5 | 0.5 |
| BA | 0.5 | 0.5 |
| BB | 1 | 0 |

=> **ABBAABABABBA...**



# Design efficiency: Conclusions

- Optimal design for one contrast may not be optimal for another
- Blocked designs generally most efficient (with short SOAs, given optimal block length is not exceeded)
- However, psychological efficiency often dictates intermixed designs, and often also sets limits on SOAs
- With randomised designs, optimal SOA for differential effect (A-B) is minimal SOA (>2 seconds, and assuming no saturation), whereas optimal SOA for main effect (A+B) is 16-20s

# Design efficiency: Conclusions

- 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)