Event-related fMRI

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FIL Methods group, Klaas Enno Stephan, Rik Henson and Christian Ruff

Methods & models for fMRI data analysis
31 October 2017

Overview of SPM

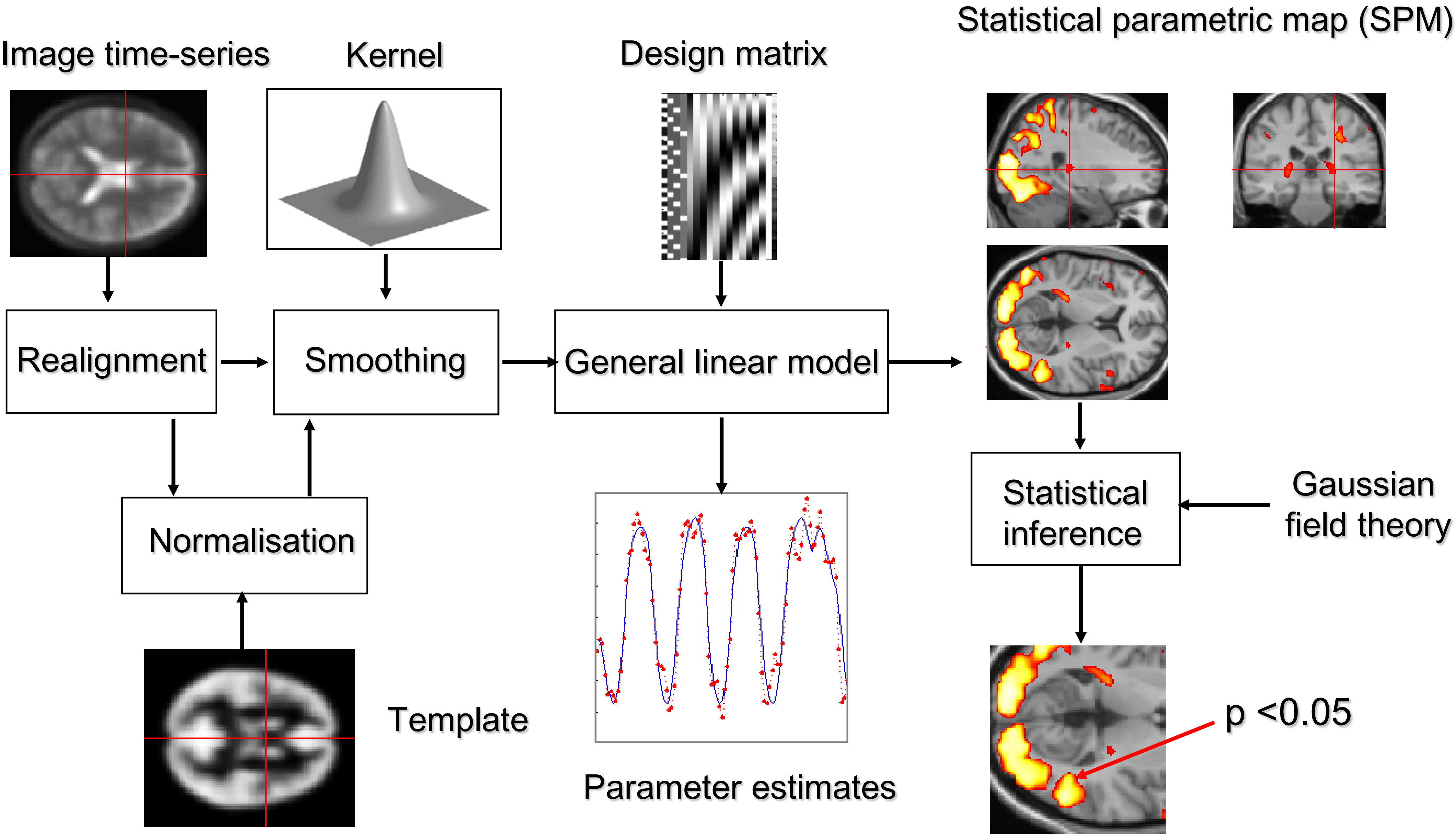


Image time-series

Kernel

Design matrix

Statistical parametric map (SPM)

Realignment

Smoothing

General linear model

Normalisation

Template

Parameter estimates

Statistical inference

Gaussian field theory

$p < 0.05$

Overview

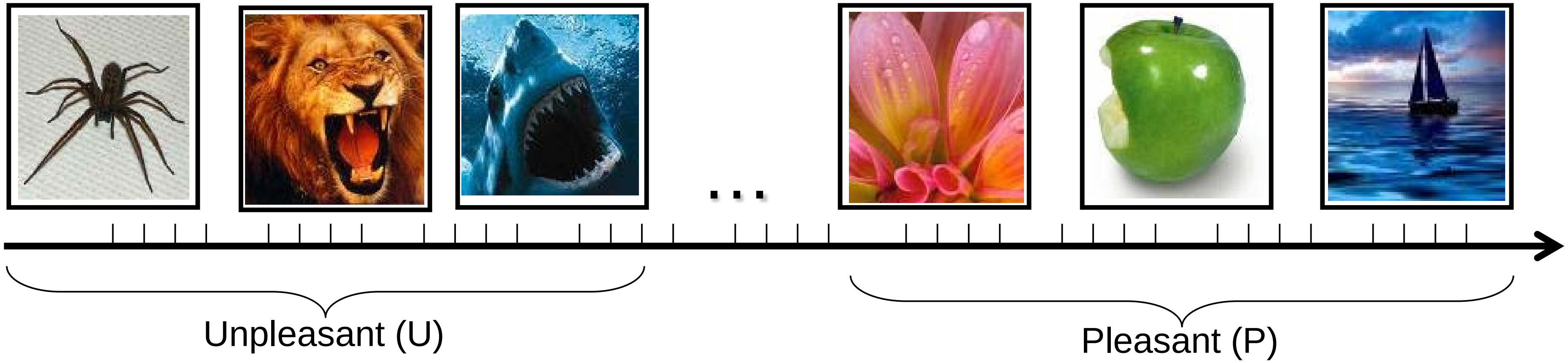
1. Advantages of er-fMRI
2. BOLD impulse response
3. General Linear Model
4. Temporal basis functions
5. Timing issues
6. Design optimisation

Advantages of er-fMRI

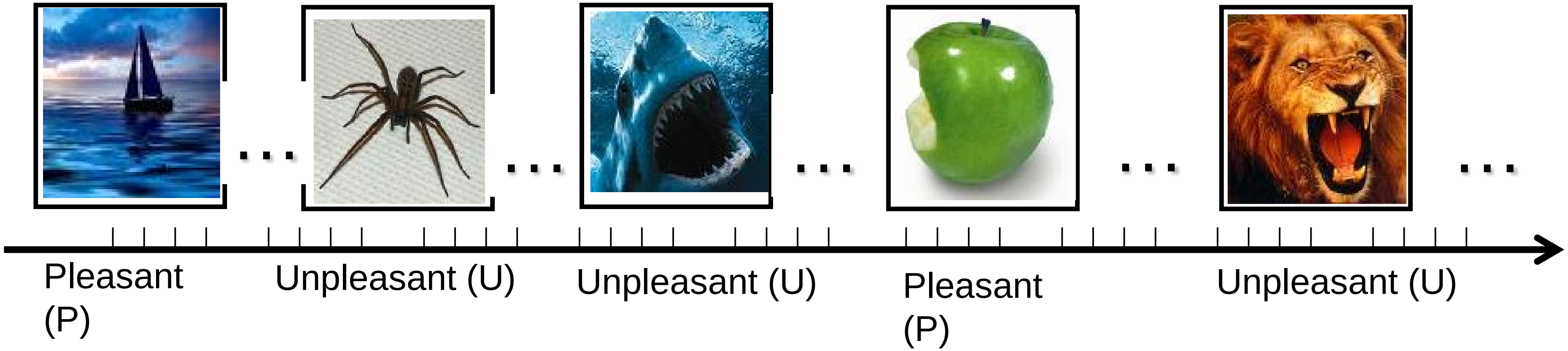
1. Randomised trial order
   cf. confounds of blocked designs

er-fMRI: Stimulus randomisation

Blocked designs may trigger expectations and cognitive sets



Intermixed designs can minimise this by stimulus randomisation

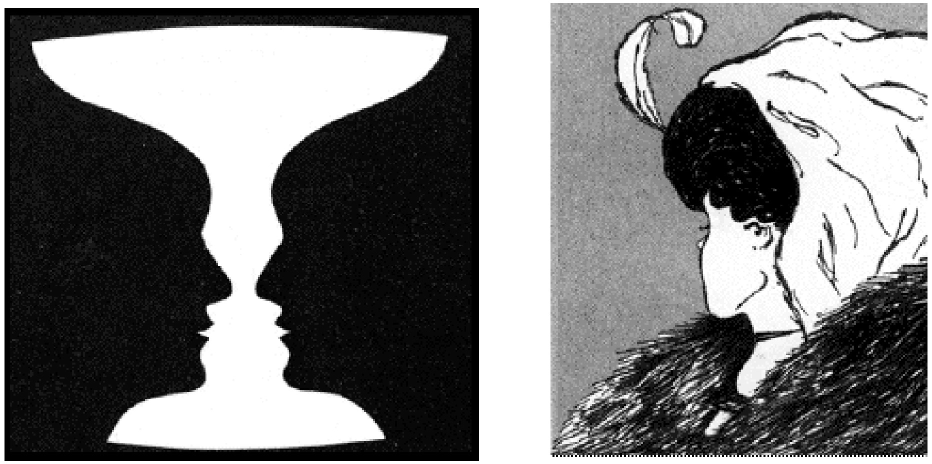


Advantages of er-fMRI

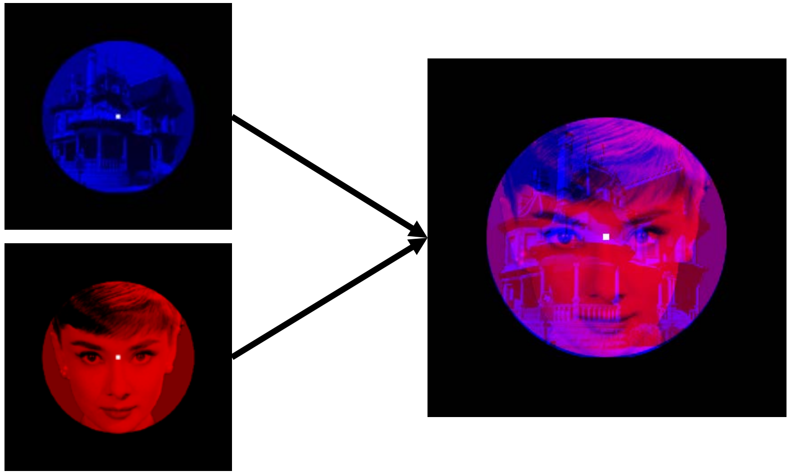
1. Randomised trial order
   cf. confounds of blocked designs
2. **Post hoc classification of trials:**
   according to performance, or because some events can only be indicated by the subject (e.g. spontaneous perceptual changes)

er-fMRI: “on-line” event-definition

Bistable percepts



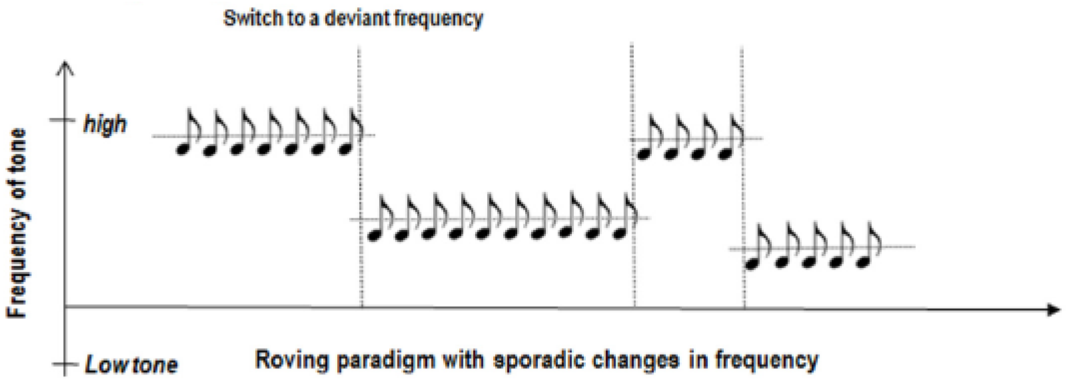
Binocular rivalry



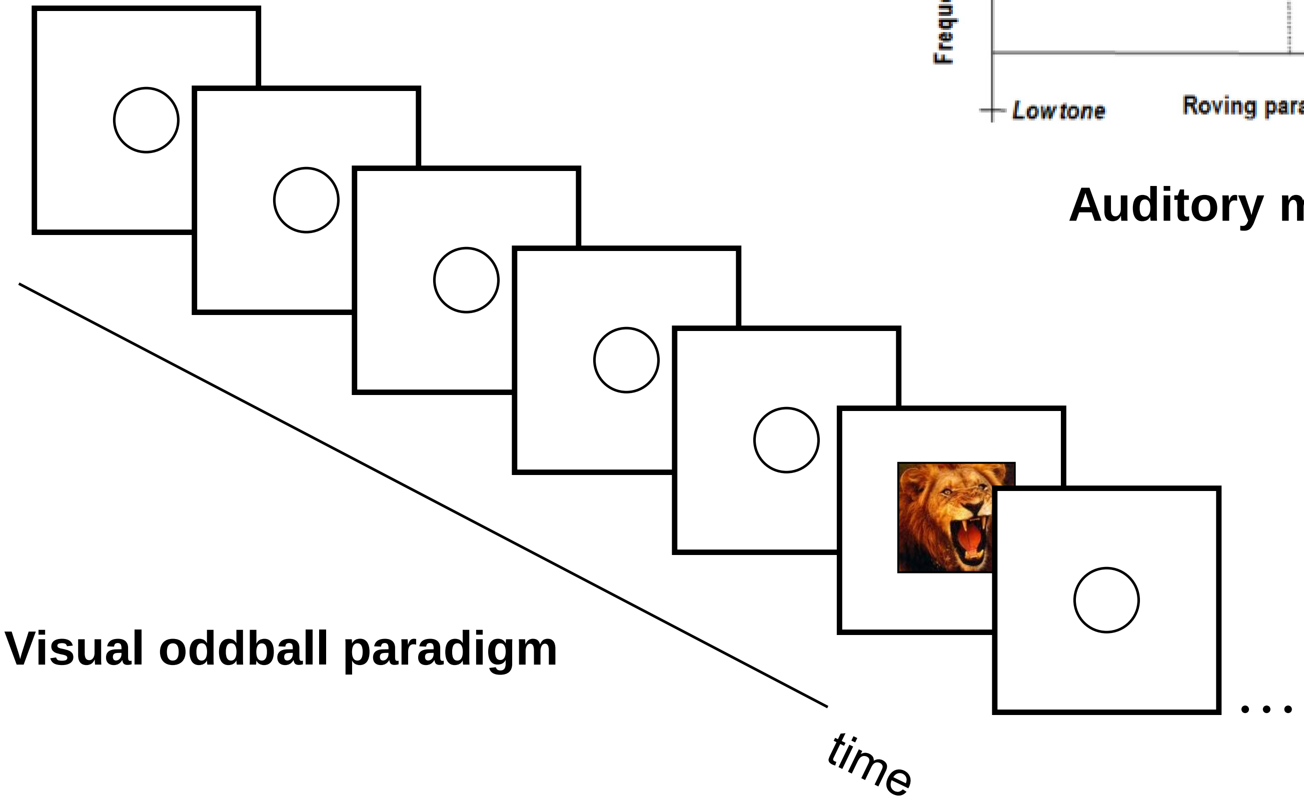
Advantages of er-fMRI

1. Randomised trial order
   cf. confounds of blocked designs
2. Post hoc classification of trials:
   according to performance, or because some events can only be indicated by the subject (e.g. spontaneous perceptual changes)
3. **Some trials cannot be blocked**
   e.g. “oddball” designs

er-fMRI: “oddball” designs



Auditory mismatch negativity (MMN)



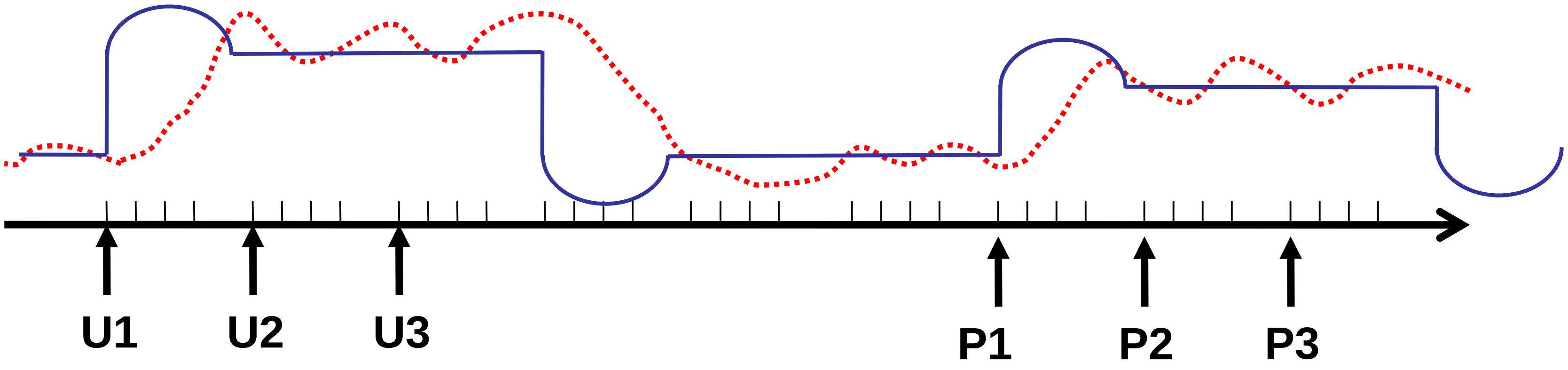
Visual oddball paradigm

Advantages of er-fMRI

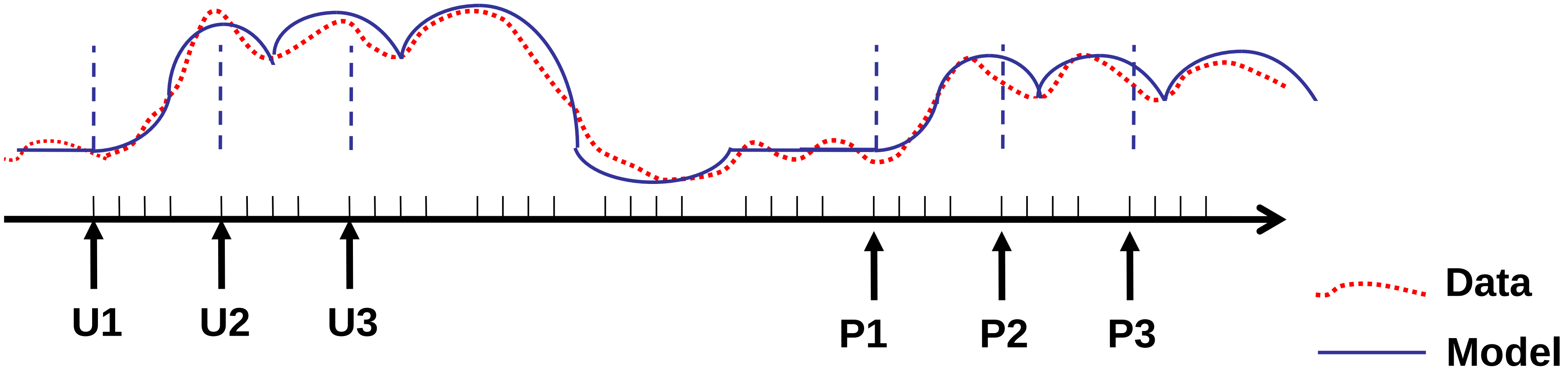
1. Randomised trial order
   cf. confounds of blocked designs
2. Post hoc classification of trials:
   according to performance, or because some events can only be indicated by the subject (e.g. spontaneous perceptual changes)
3. Some trials cannot be blocked
   e.g. “oddball” designs
4. **More accurate models even for blocked designs?**

er-fMRI: “event-based” model of block-designs

“Epoch” model assumes constant neural processes throughout block



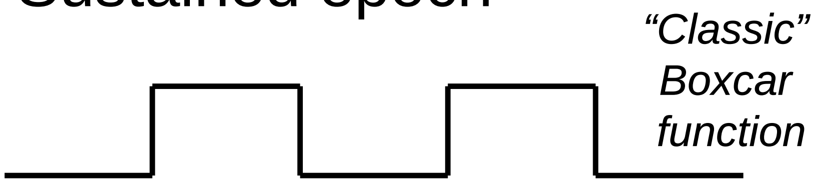
“Event” model may capture response better



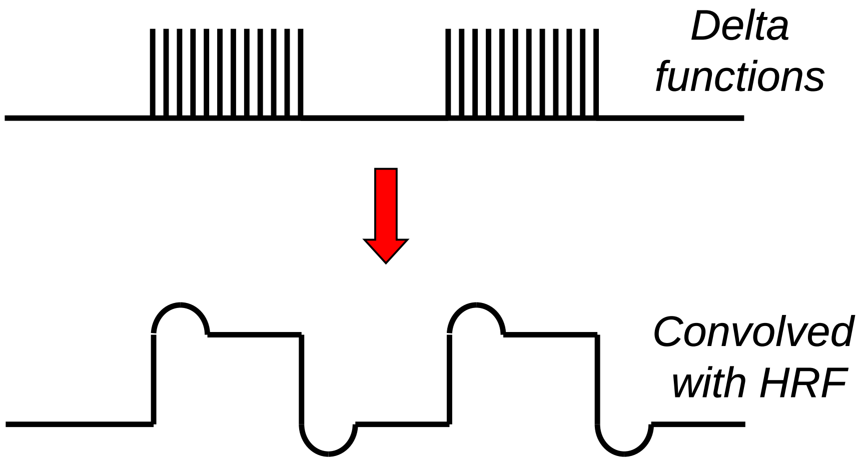
Modeling block designs: epochs vs events

- *Models for ER designs are based on events* (delta functions)...
- ... but models for blocked designs can be epoch- or event-related
- Near-identical regressors can be created by 1) sustained epochs, 2) rapid series of events (SOAs<~3s)
- In SPM, all conditions are specified in terms of their 1) onsets and 2) durations
  - epochs: variable or constant duration, unit amplitude
  - events: zero duration, amplitude: 1/dt

Sustained epoch



Series of events



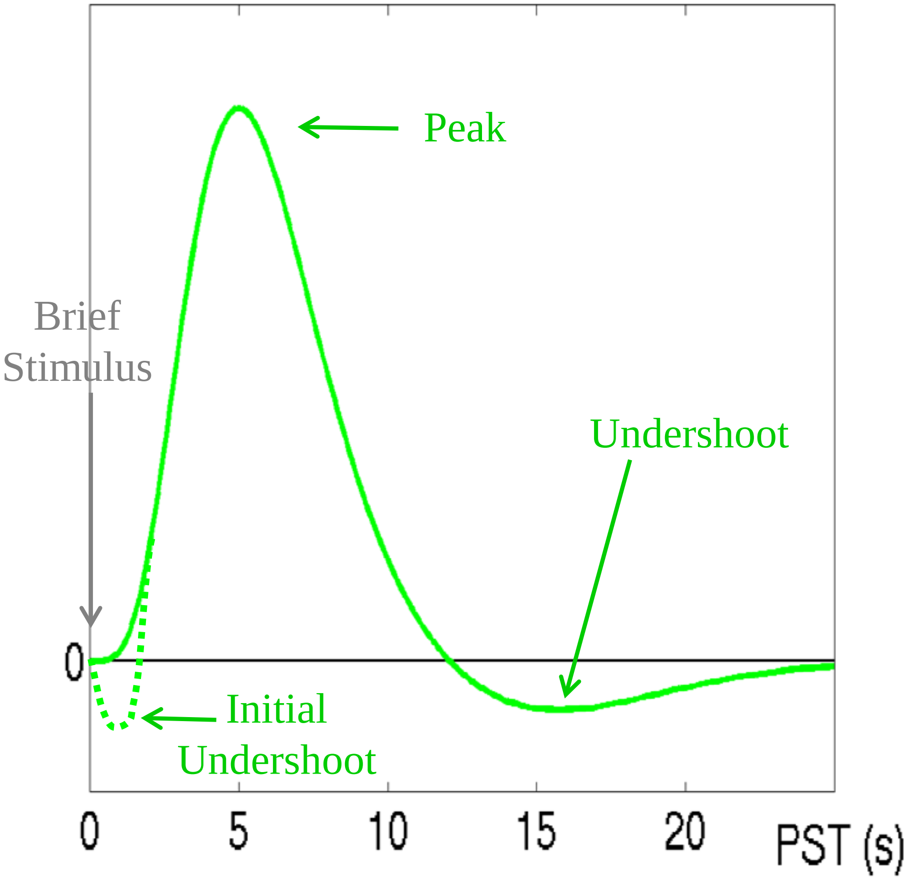
Disadvantages of er-fMRI

1. Less efficient for detecting effects than blocked designs (discussed in detail later).

2. Some psychological processes may be better blocked (e.g. task-switching, attentional instructions).

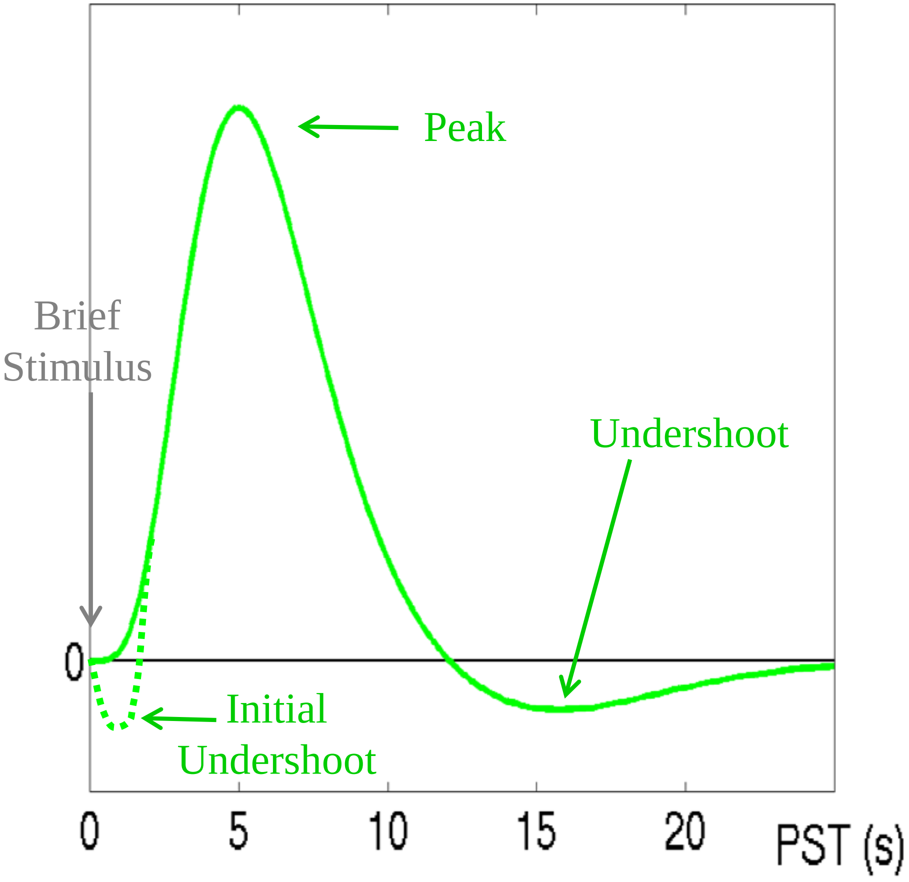
BOLD impulse response

- Function of blood volume and deoxyhemoglobin content (Buxton et al. 1998)
- Peak (max. oxygenation) 4-6s post-stimulus; return to baseline after 20-30s
- initial undershoot sometimes observed (Malonek & Grinvald, 1996)
- Similar across V1, A1, S1…
- … but differences across other regions (Schacter et al. 1997) and individuals (Aguirre et al. 1998)

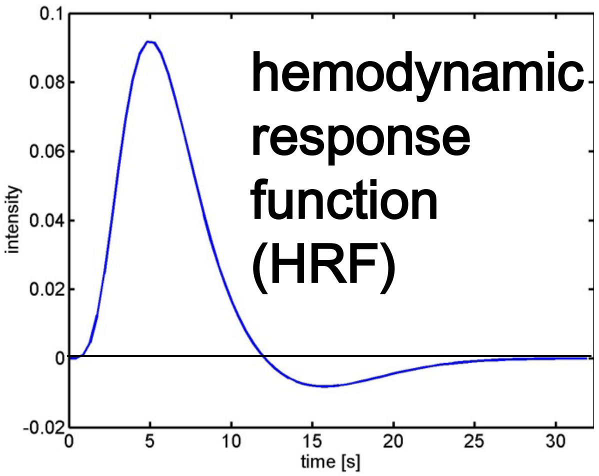


BOLD impulse response

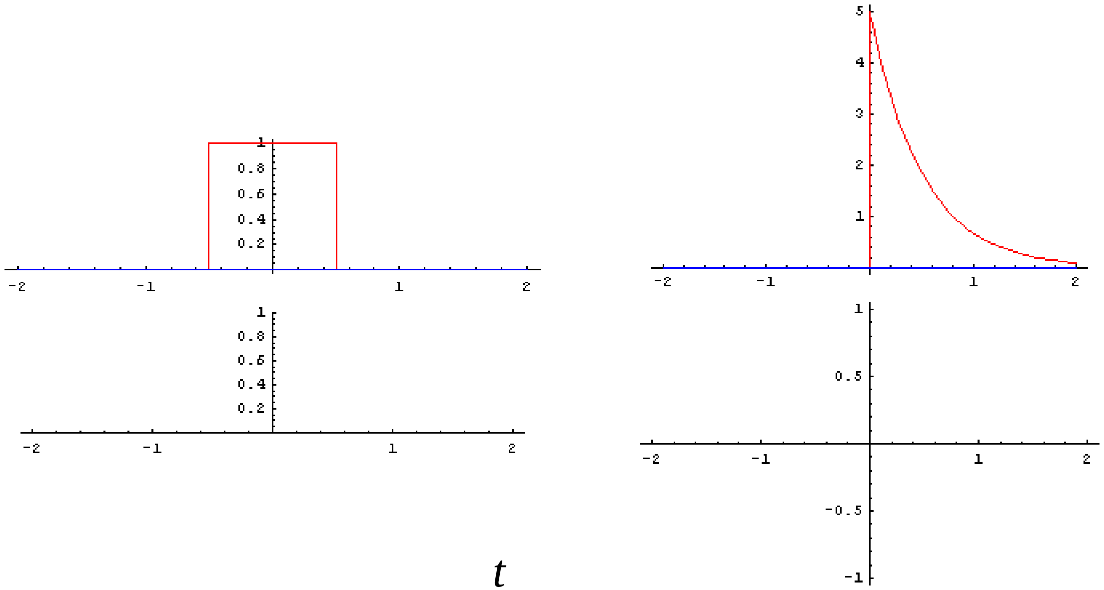
- Early er-fMRI studies used a long Stimulus Onset Asynchrony (SOA) to allow BOLD response to return to baseline.
- However, if the BOLD response is explicitly modelled, overlap between successive responses at short SOAs can be accommodated…
- … particularly if responses are assumed to superpose linearly.
- Short SOAs can give a more efficient design (see below).



Reminder: BOLD response as output from LTI



hemodynamic response function (HRF)



$$f \otimes g(t) = \int_0^t f(\tau) g(t-\tau) d\tau$$

The response of a linear time-invariant (LTI) system is the convolution of the input with the system's response to an impulse (delta function).

expected BOLD response

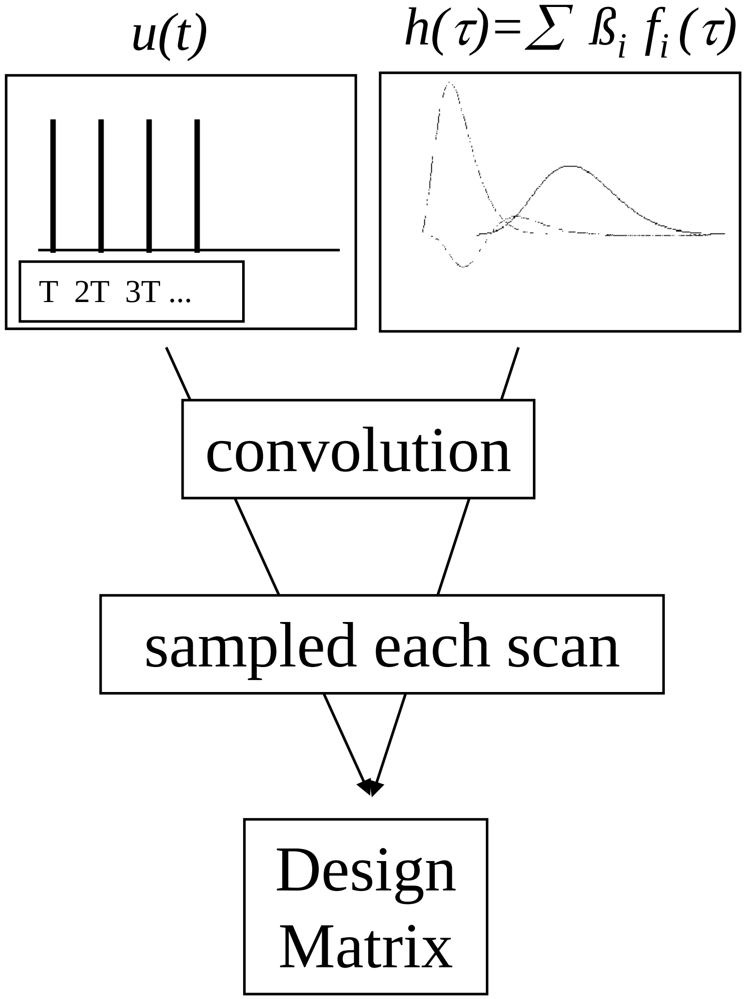
= input function ⊗ impulse response function (HRF)

General Linear (Convolution) Model

For block designs, the exact shape of the convolution kernel (i.e. HRF) does not matter much.

For event-related designs this becomes much more important.

Usually, we use more than a single basis function to model the HRF.


$u(t)$

$h(\tau)=\sum ß_i \, f_i(\tau)$

convolution

sampled each scan

Design Matrix

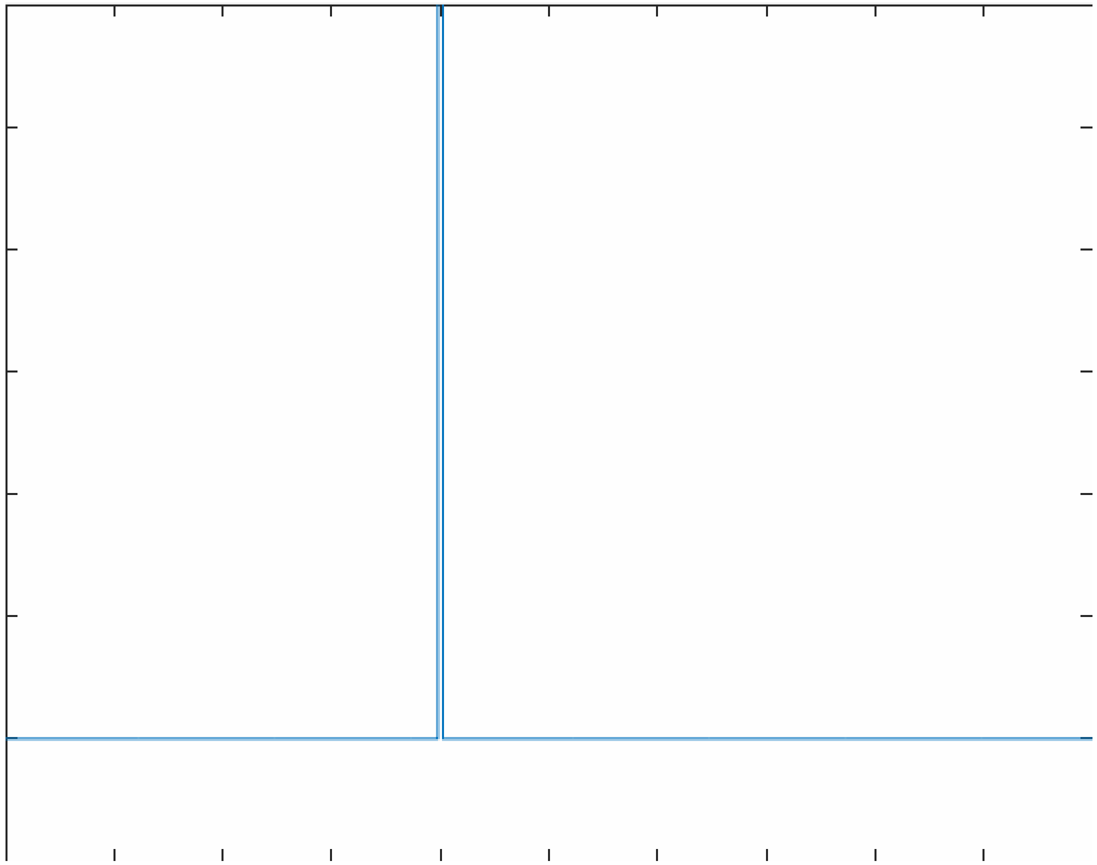
GLM for a single voxel:

$$\mathbf{y(t)} = [\mathbf{u(t)} \otimes \mathbf{h(\tau)}]\boldsymbol{\beta} + \mathbf{e(t)}$$

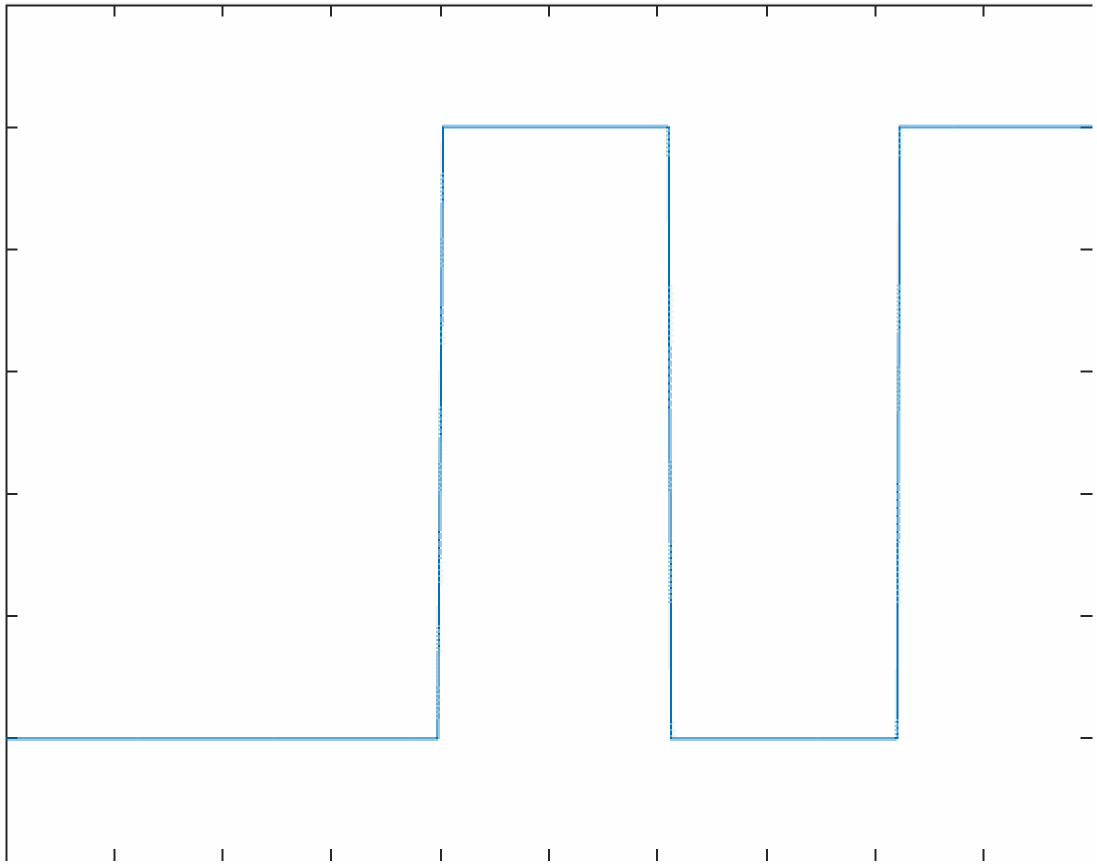
Omitting time index:

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

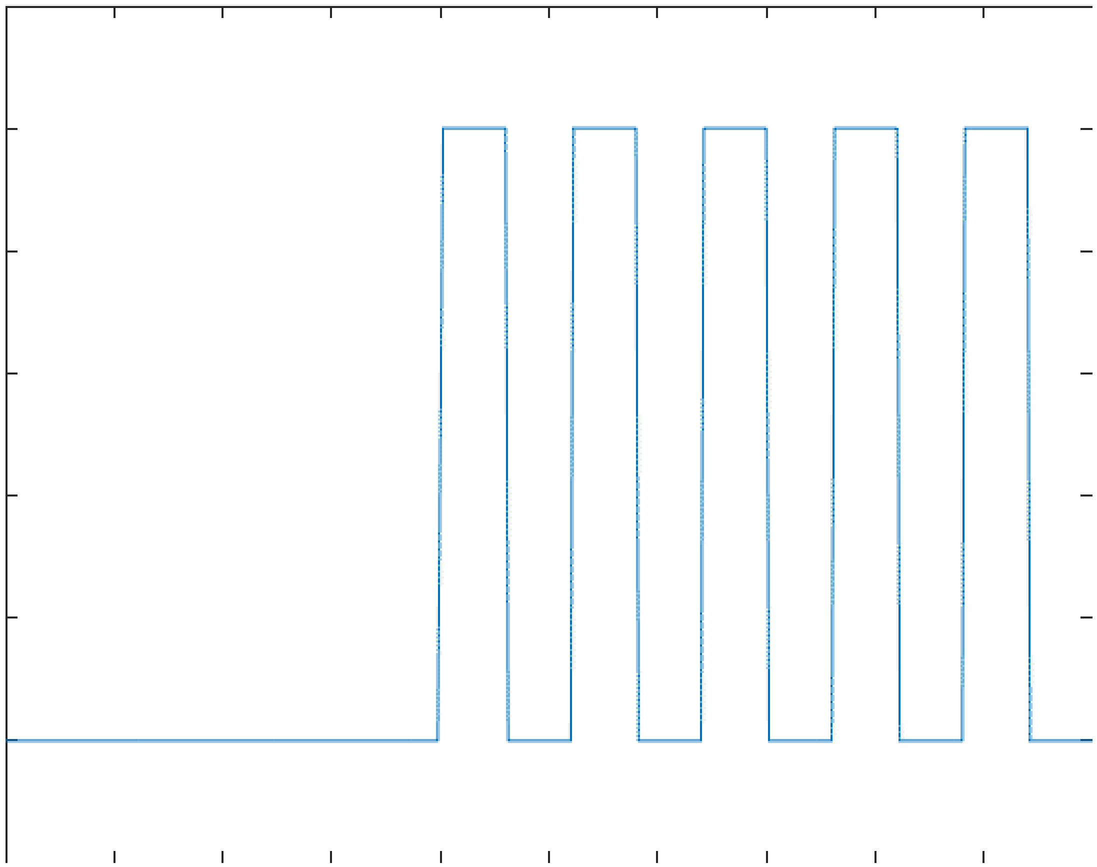
Convolution with BOLD 1



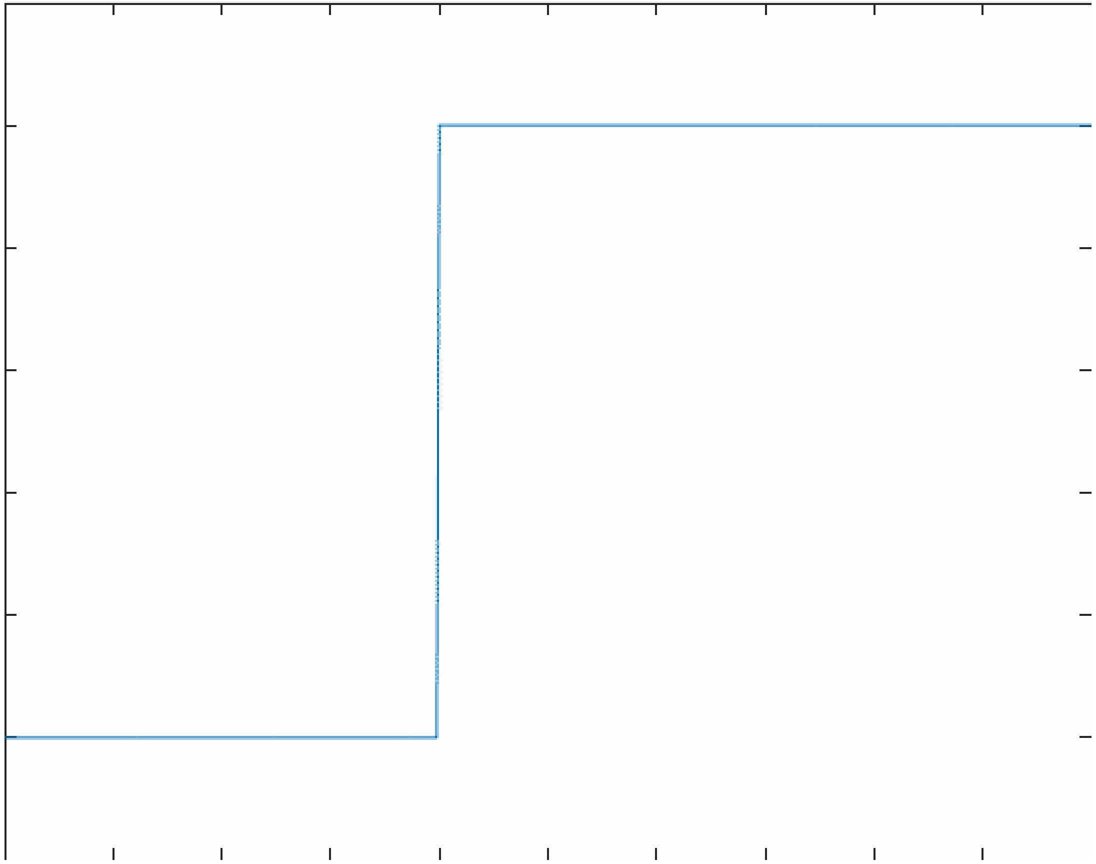
Convolution with BOLD 2



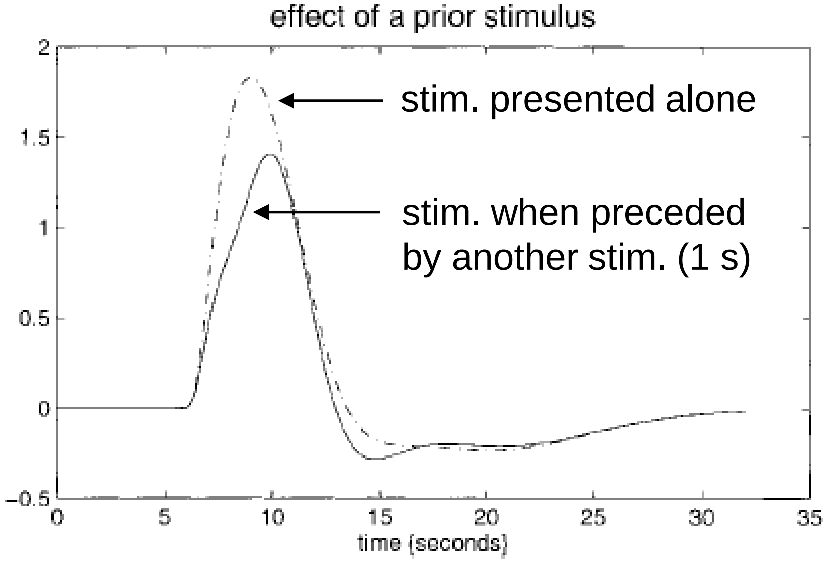
Convolution with BOLD 3



Convolution with BOLD 4



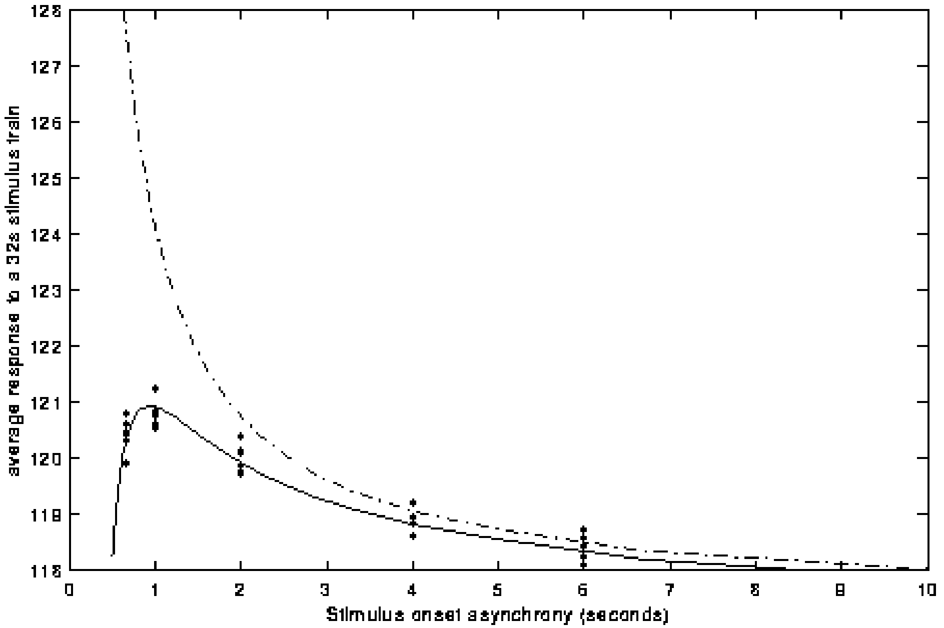
Nonlinearities at short SOAs



stim. presented alone

stim. when preceded
by another stim. (1 s)

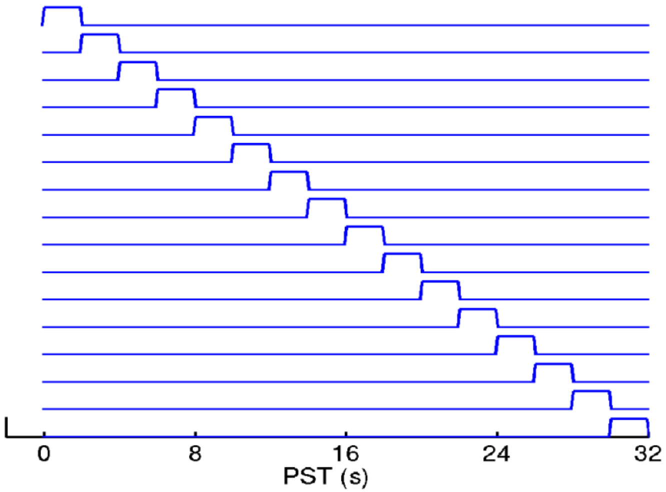
Friston et al. 2000, *NeuroImage*



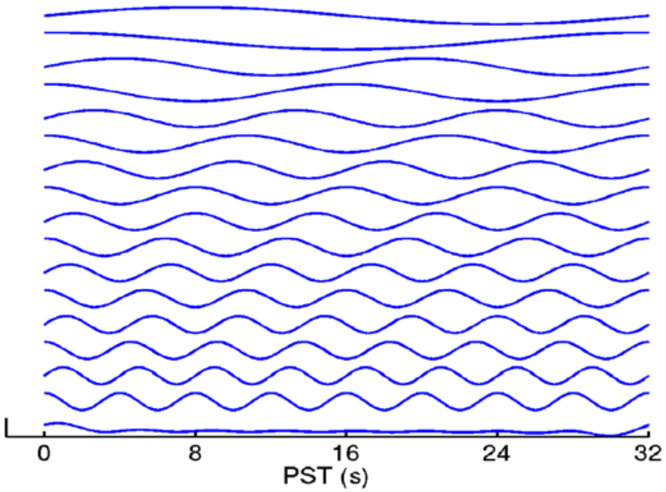
Friston et al. 1998, *Magn. Res. Med.*

Temporal basis functions

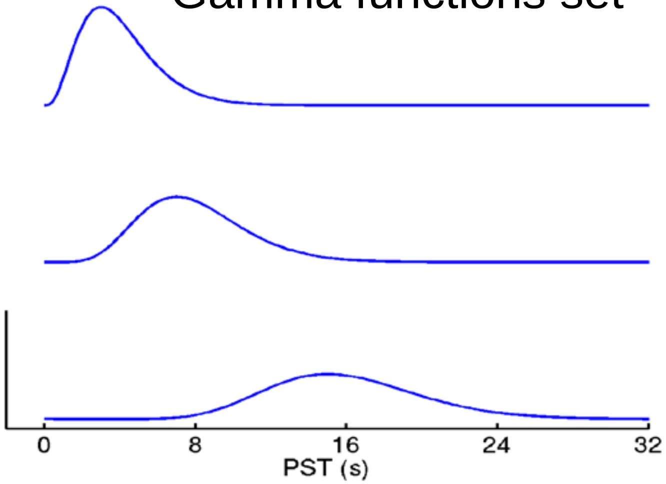
Finite Impulse Response (FIR) model



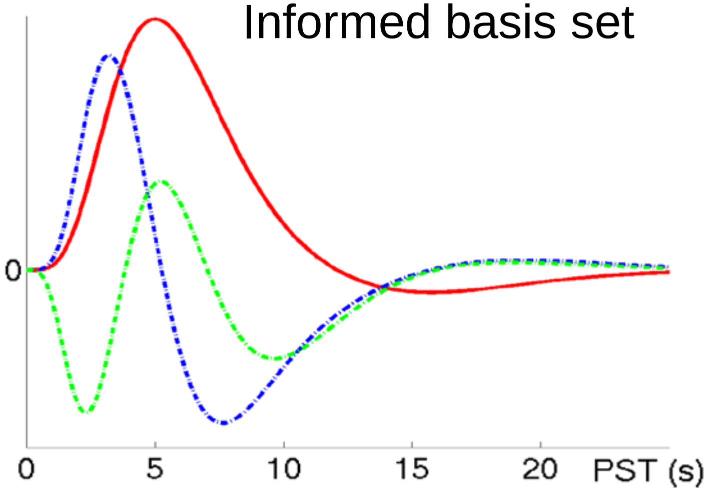
Fourier basis set



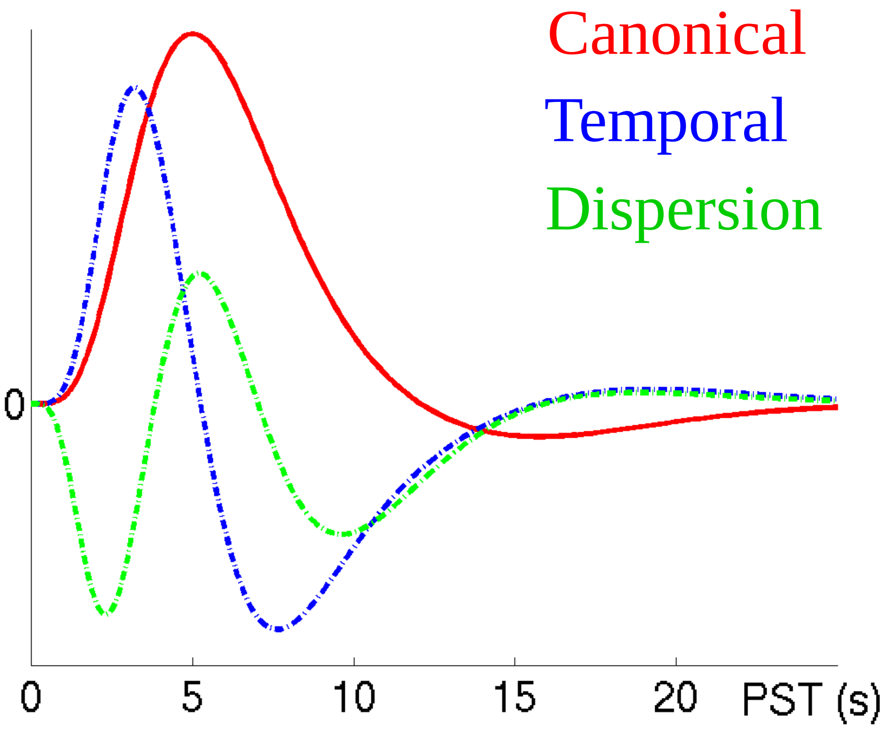
Gamma functions set



Informed basis set



Informed basis set

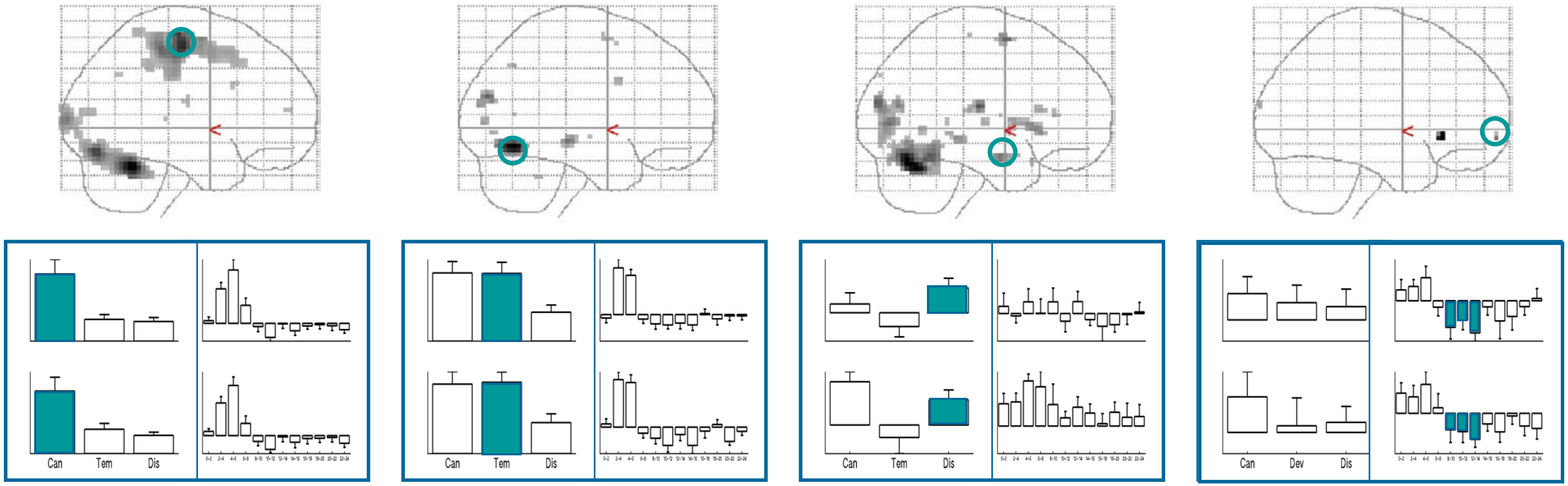


Friston et al. 1998, *NeuroImage*

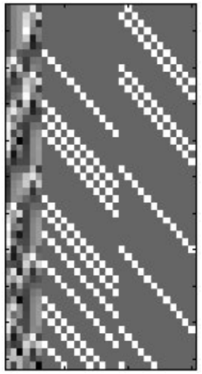
- Canonical HRF:
  - linear combination of 2 gamma functions
  - 7 parameters, see spm_hrf
- *plus* multivariate Taylor expansion in:
  - time (*Temporal Derivative*)
  - width (*Dispersion Derivative;* partial derivative of canonical HRF wrt. parameter controlling the width)
- F-tests: testing for responses of any shape.
- T-tests on canonical HRF alone (at 1st level) can be improved by derivatives reducing residual error, and can be interpreted as “amplitude” differences, assuming canonical HRF is a reasonable fit.

Temporal basis sets: Which one?

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



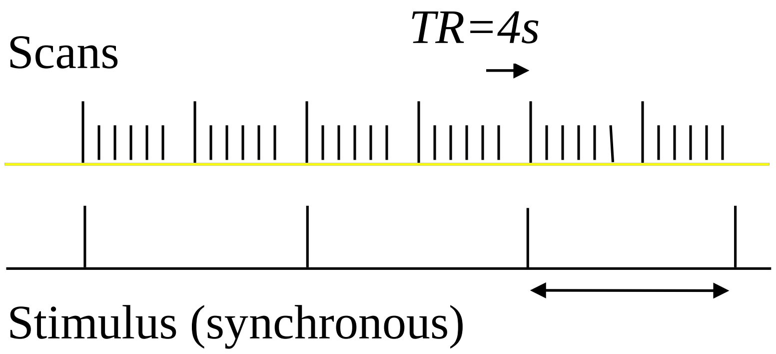
Canonical **+ Temporal** **+ Dispersion** **+ FIR**

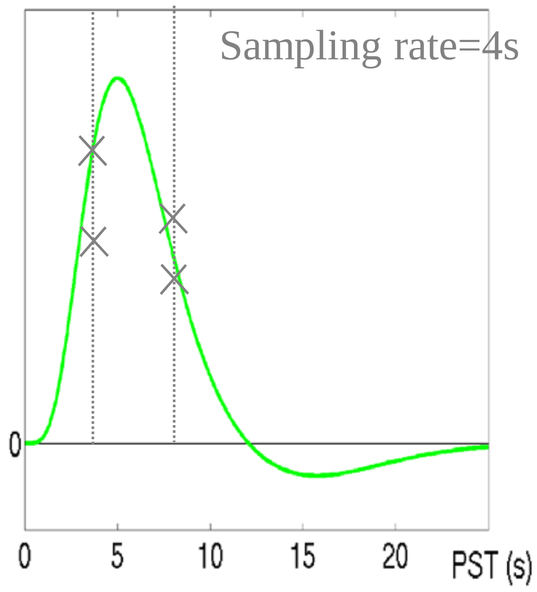


- canonical + temporal + dispersion derivatives appear sufficient
- may not be for more complex trials (e.g. stimulus-delay-response)
- but then such trials better modelled with separate neural components (i.e. activity no longer delta function) (Zarahn, 1999)

Timing Issues : Practical

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

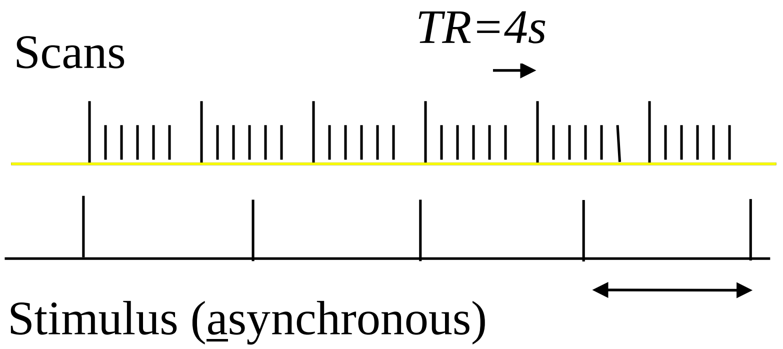




SOA = Stimulus onset asynchrony
(= time between onsets of two subsequent stimuli)

Timing Issues : Practical

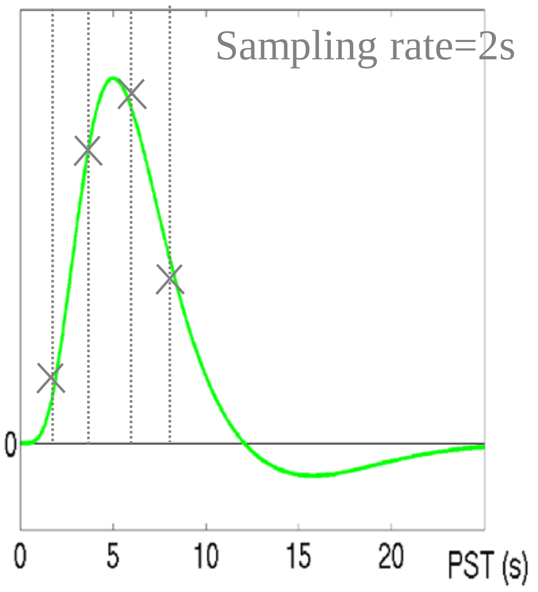
- Assume TR is 4s
- Sampling at [0,4,8,12…] post- stimulus may miss peak signal
- Higher effective sampling by:
  - 1. Asynchrony, *e.g. SOA* = 1.5×TR



Scans

TR=4s

Stimulus (asynchronous)



SOA = Stimulus onset asynchrony
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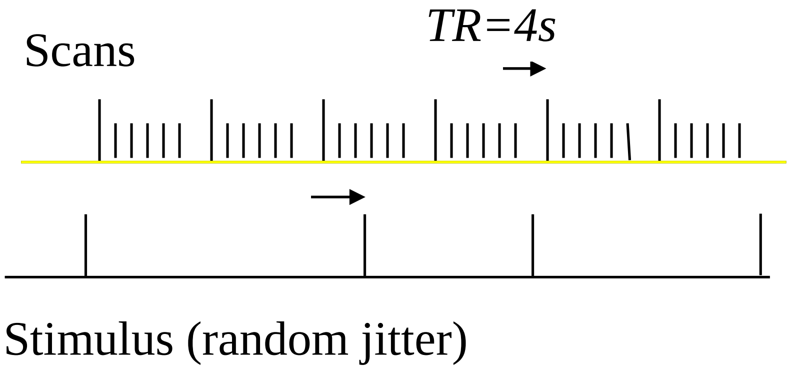
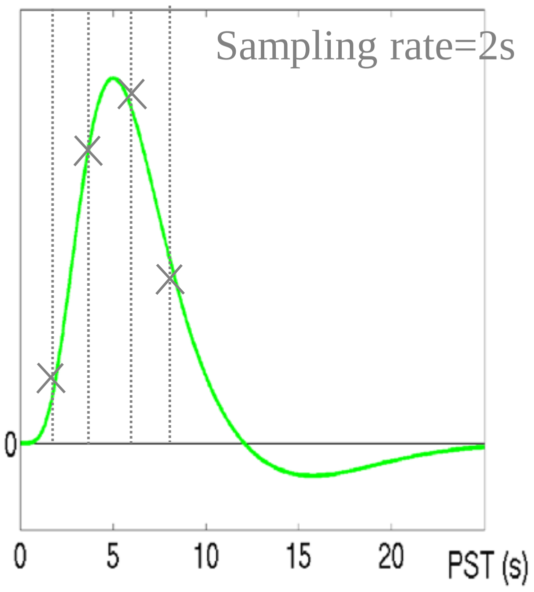
Timing Issues : Practical

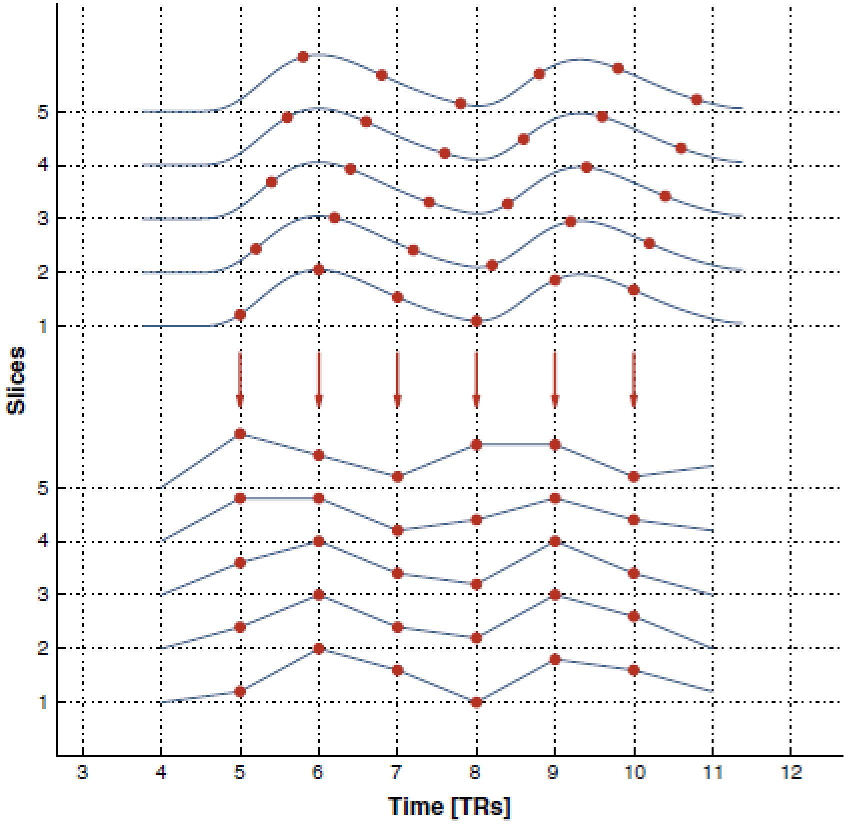
- Assume TR is 4s
- Sampling at [0,4,8,12…] post- stimulus may miss peak signal
- Higher effective sampling by:
  - 1. Asynchrony, *e.g. SOA* = 1.5×TR
  - 2. Random jitter, e.g. SOA = (2 ± 0.5)×TR
- Better response characterisation (Miezin et al, 2000)

SOA = Stimulus onset asynchrony
(= time between onsets of two subsequent stimuli)





Slice-timing



Sladky et al. 2011, NeuroImage

Slice-timing

- Slices acquired at different times, yet model is the same for all slices

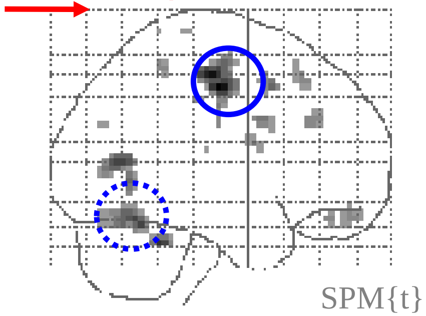
  => *different results (using canonical HRF) for different reference slices*

- Solutions:

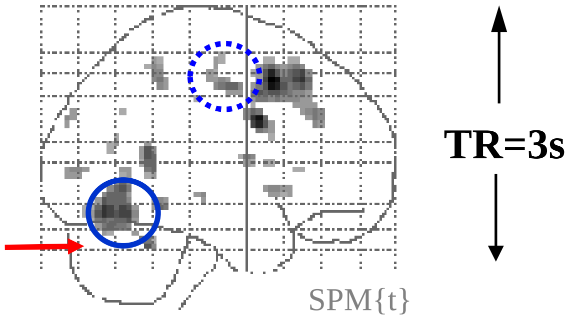
1. Temporal interpolation of data
   … but may be problematic for longer TRs

2. More general basis set (e.g. with temporal derivatives)
   … but more complicated design matrix

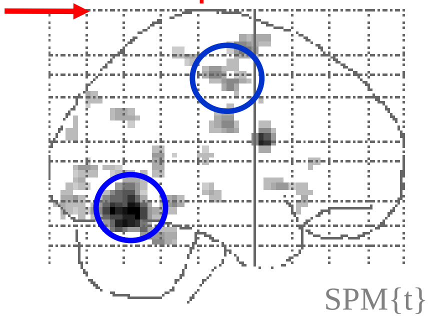
Top slice



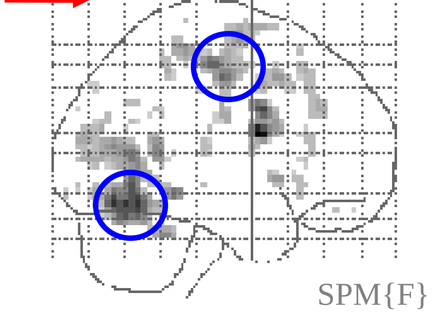
Bottom slice



Interpolated



Derivative



Henson et al. 1999

Design efficiency

How can I make my experimental design as good (powerful) as possible?

Design efficiency

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

- **The aim is to minimize the standard error of a *t*-contrast (i.e. the denominator of a t-statistic).**

$$\mathrm{var}(c^T \hat{\beta}) = \hat{\sigma}^2 c^T (X^T X)^{-1} c$$

- **This is equivalent to maximizing the efficiency *e*:**

$$e(\hat{\sigma}^2, c, X) = (\underbrace{\hat{\sigma}^2}_{\textbf{Noise variance}} c^T \underbrace{(X^T X)}_{\textbf{Design variance}}{}^{-1} c)^{-1}$$

- **If we assume that the noise variance is independent of the specific design:**

$$e(c, X) = (c^T (X^T X)^{-1} c)^{-1}$$

- **This is a relative measure: all we can really say is that one design is more efficient than another (for a given contrast).**

Scaling issues – a x c

$$T = \frac{c^T \hat{\beta}}{\sqrt{\mathrm{var}(c^T \hat{\beta})}} = \frac{c^T \hat{\beta}}{\sqrt{\hat{\sigma}^2 c^T \left(X^T X\right)^{-1} c}}$$

$$T_a = \frac{ac^T \hat{\beta}}{\sqrt{\mathrm{var}(ac^T \hat{\beta})}} = \frac{ac^T \hat{\beta}}{\sqrt{\hat{\sigma}^2 ac^T \left(X^T X\right)^{-1} ac}} = \frac{c^T \hat{\beta}}{\sqrt{\hat{\sigma}^2 c^T \left(X^T X\right)^{-1} c}} = T$$

Multiplying the contrast with a scalar does not change the t-value?

Scaling issues – b x X

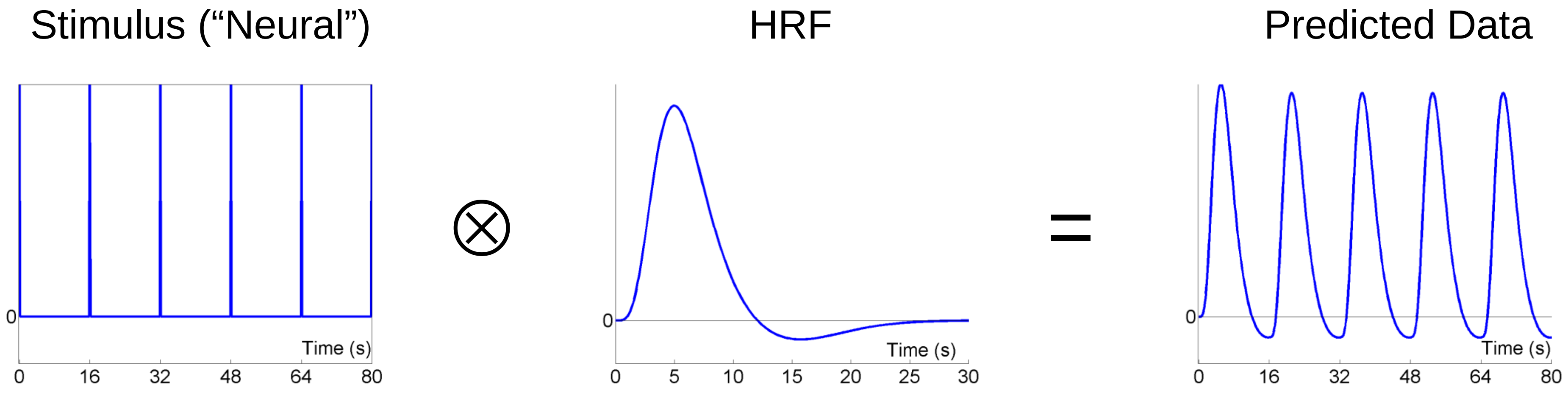
$$T_b = \frac{c^T \hat{\beta}_b}{\sqrt{\mathrm{var}(c^T \hat{\beta}_b)}} = \frac{c^T \hat{\beta}_b}{\sqrt{\hat{\sigma}^2 c^T \left(bX^T bX\right)^{-1} c}}$$

$$\widehat{\beta_b} = (bX^T bX)^{-1} bX^T y = \hat{\beta}/b$$

$$T_b = \frac{c^T \hat{\beta} / b}{b^{-1} \sqrt{\hat{\sigma}^2 c^T \left(X^T X\right)^{-1} c}} = T$$

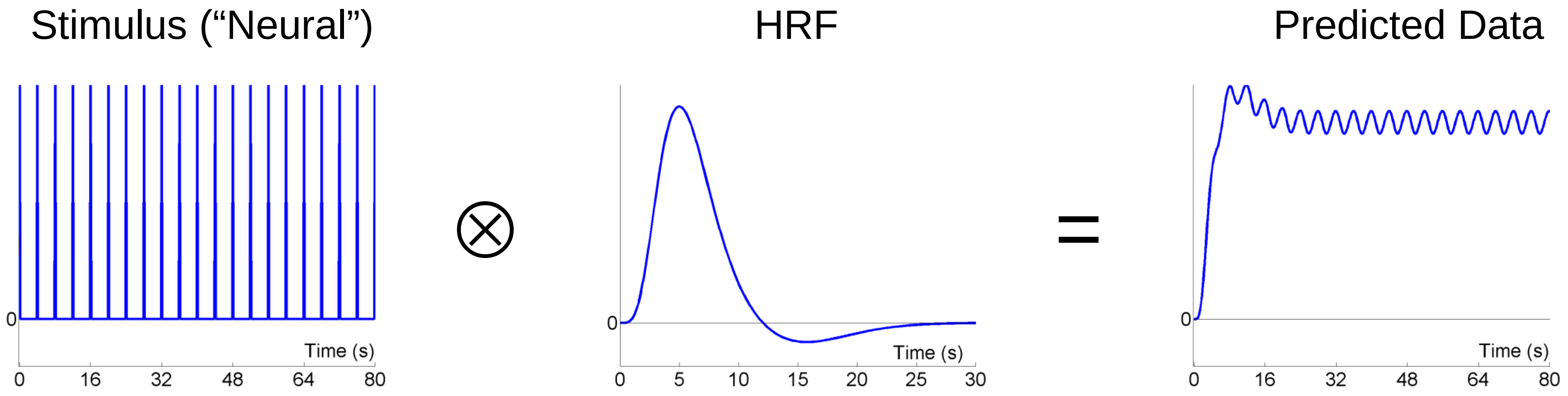
Multiplying the design matrix with a scalar does not change the t-value?

Fixed SOA = 16s



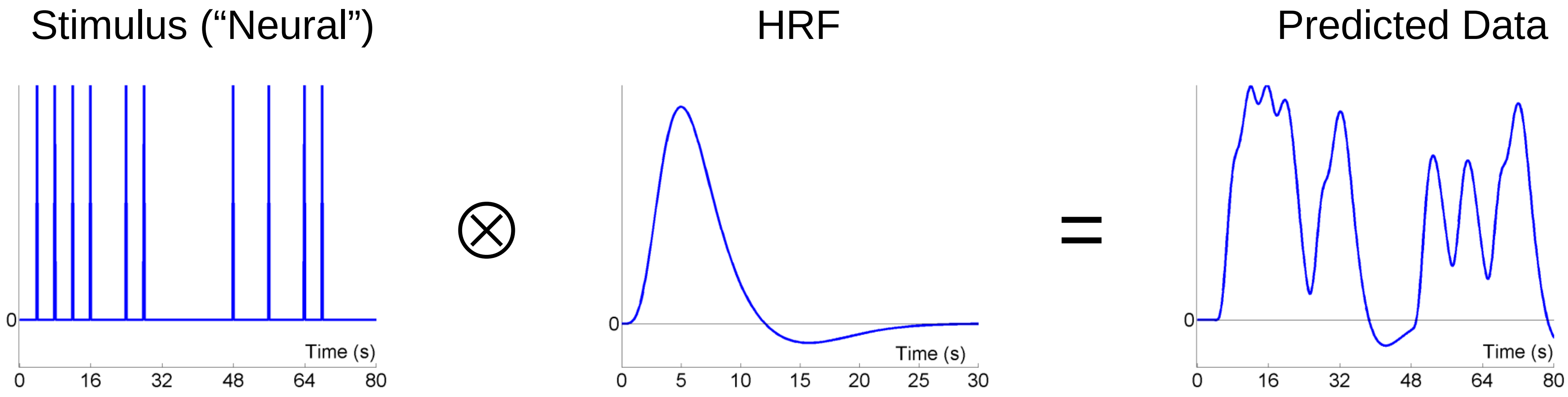
Not particularly efficient…

Fixed SOA = 4s



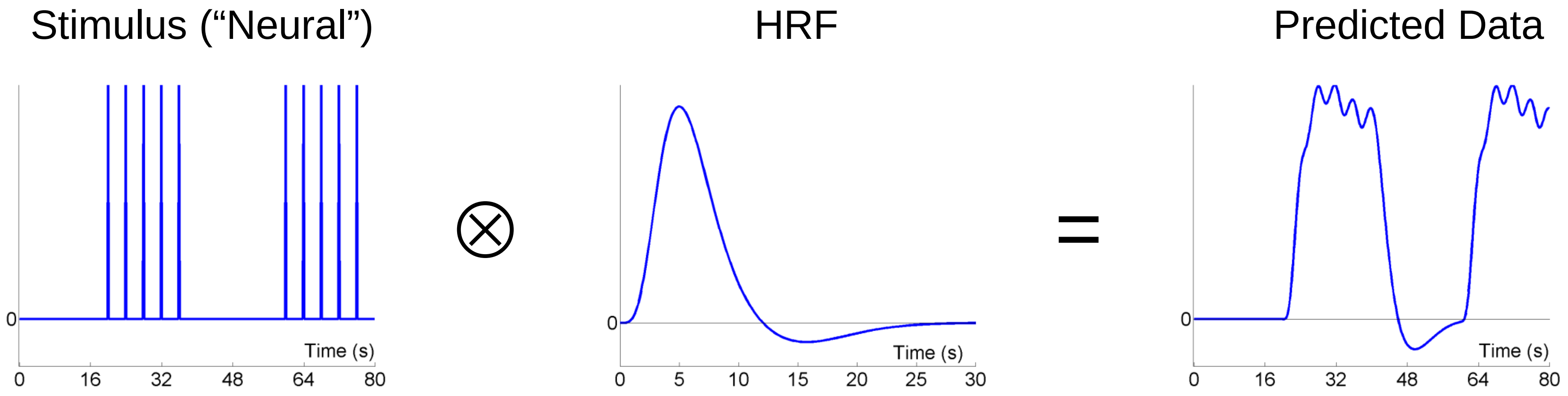
Very inefficient…

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



More efficient …

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

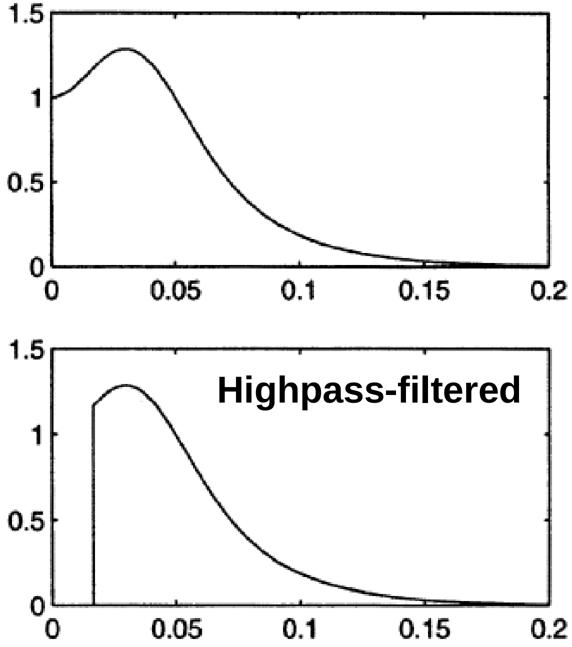


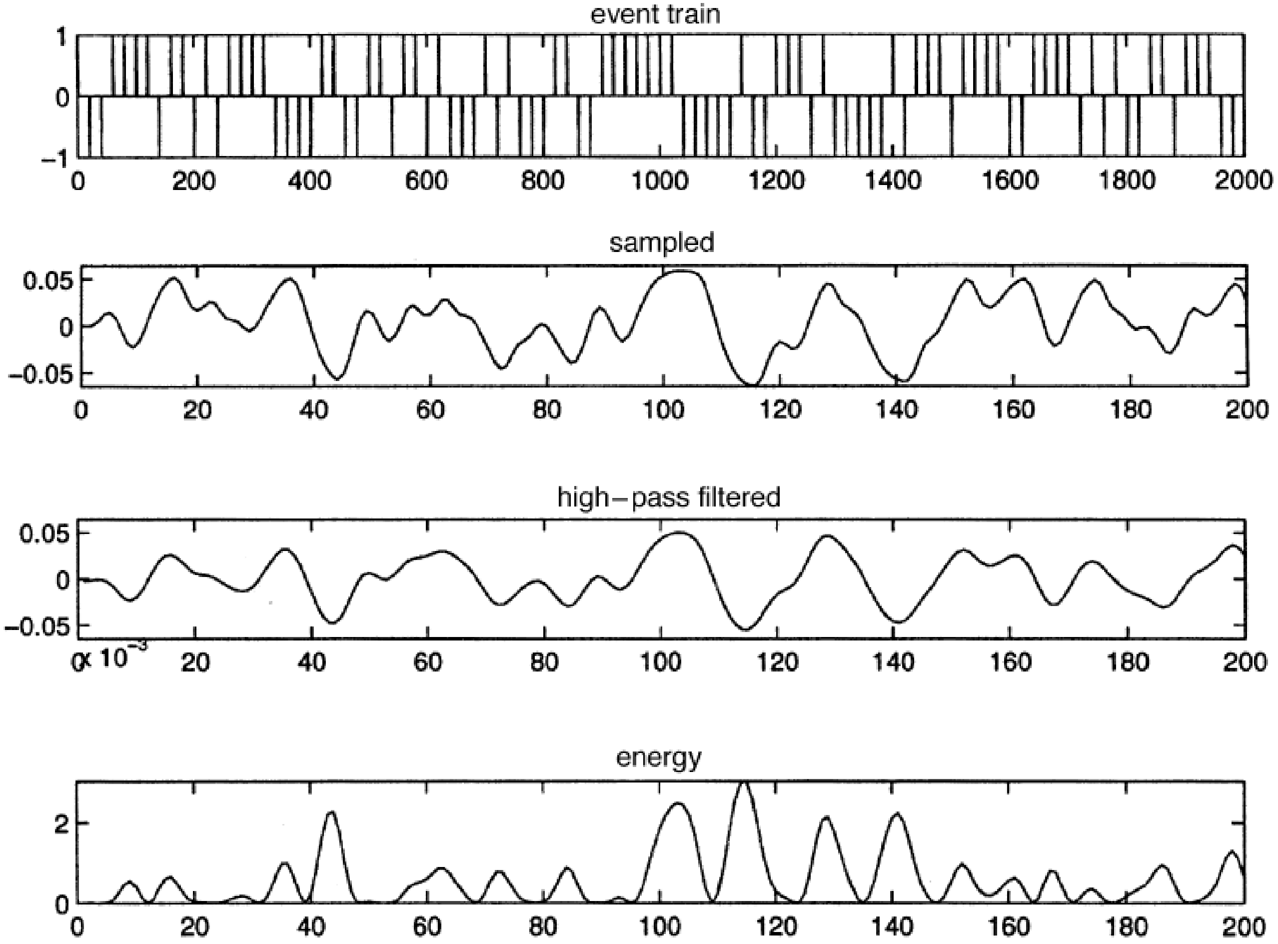
Even more efficient…

Another perspective on efficiency

Hemodynamic transfer function

(based on canonical HRF)**:**
neural activity (Hz) → BOLD



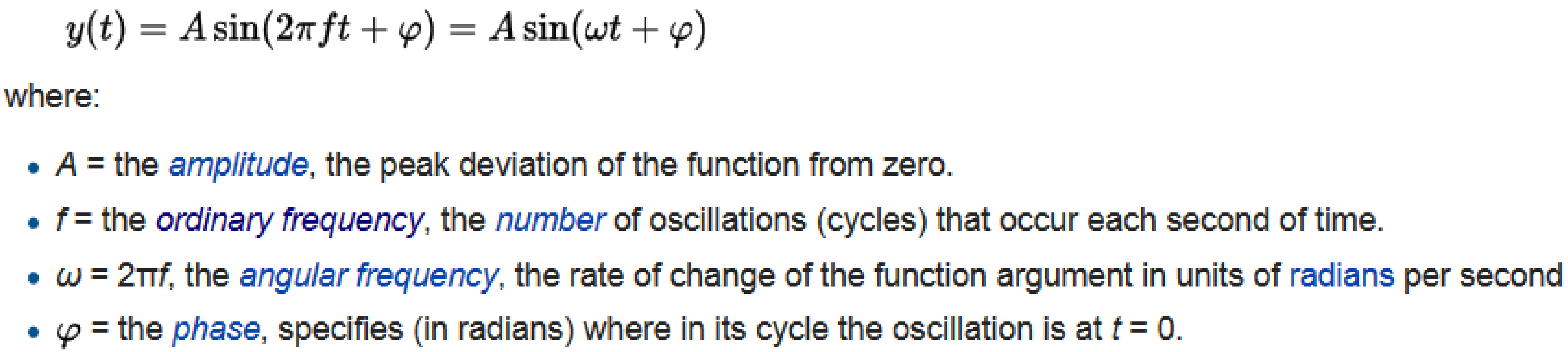


efficiency = bandpassed signal energy

Josephs & Henson 1999, *Phil Trans B*

Fourier series

Sine wave



$$y(t) = A\sin(2\pi ft + \varphi) = A\sin(\omega t + \varphi)$$

where:

- A = the *amplitude*, the peak deviation of the function from zero.
- f = the *ordinary frequency*, the *number* of oscillations (cycles) that occur each second of time.
- $\omega = 2\pi f$, the *angular frequency*, the rate of change of the function argument in units of radians per second
- φ = the *phase*, specifies (in radians) where in its cycle the oscillation is at $t = 0$.

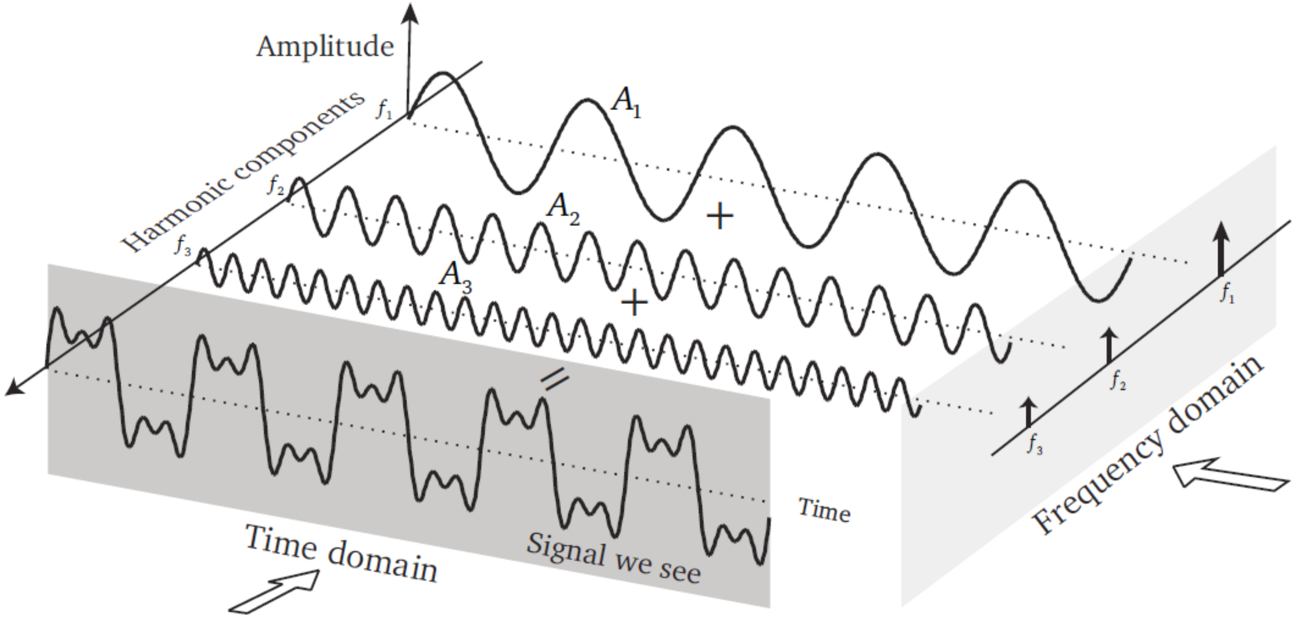
Power = squared amplitude (often represented in logs)

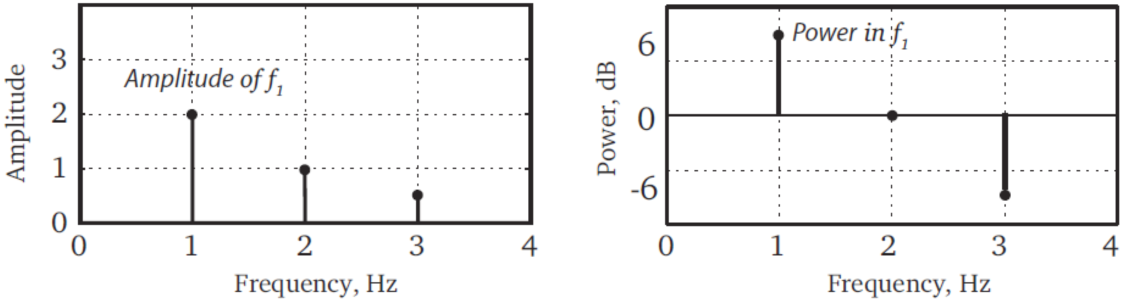
Signal energy = integral of power over time

Fourier series
= infinite sum of sines and
cosines of different frequencies

$$\boxed{f(t) = a_0 + \sum_{k=1}^{\infty} a_k \cos(2\pi f_k t) + \sum_{k=1}^{\infty} b_k \sin(2\pi f_k t)}$$

Fourier series





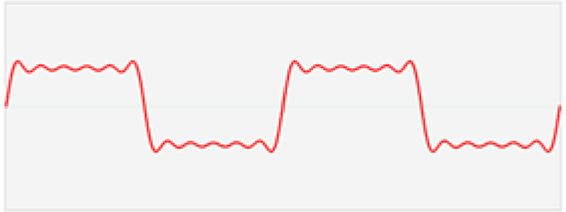
(a) Amplitude spectrum

(b) Power spectrum

Langton & Levin (2016) Intuitive Guide to Fourier Analysis

Fourier transform

- simply speaking, the Fourier transform F provides the Fourier series coefficients for a signal, i.e., it decomposes a function of time (a signal) into the frequencies it consists of
- linear operator
- convolution in time domain = multiplication in frequency domain: F(f*g) = F(f)F(g)



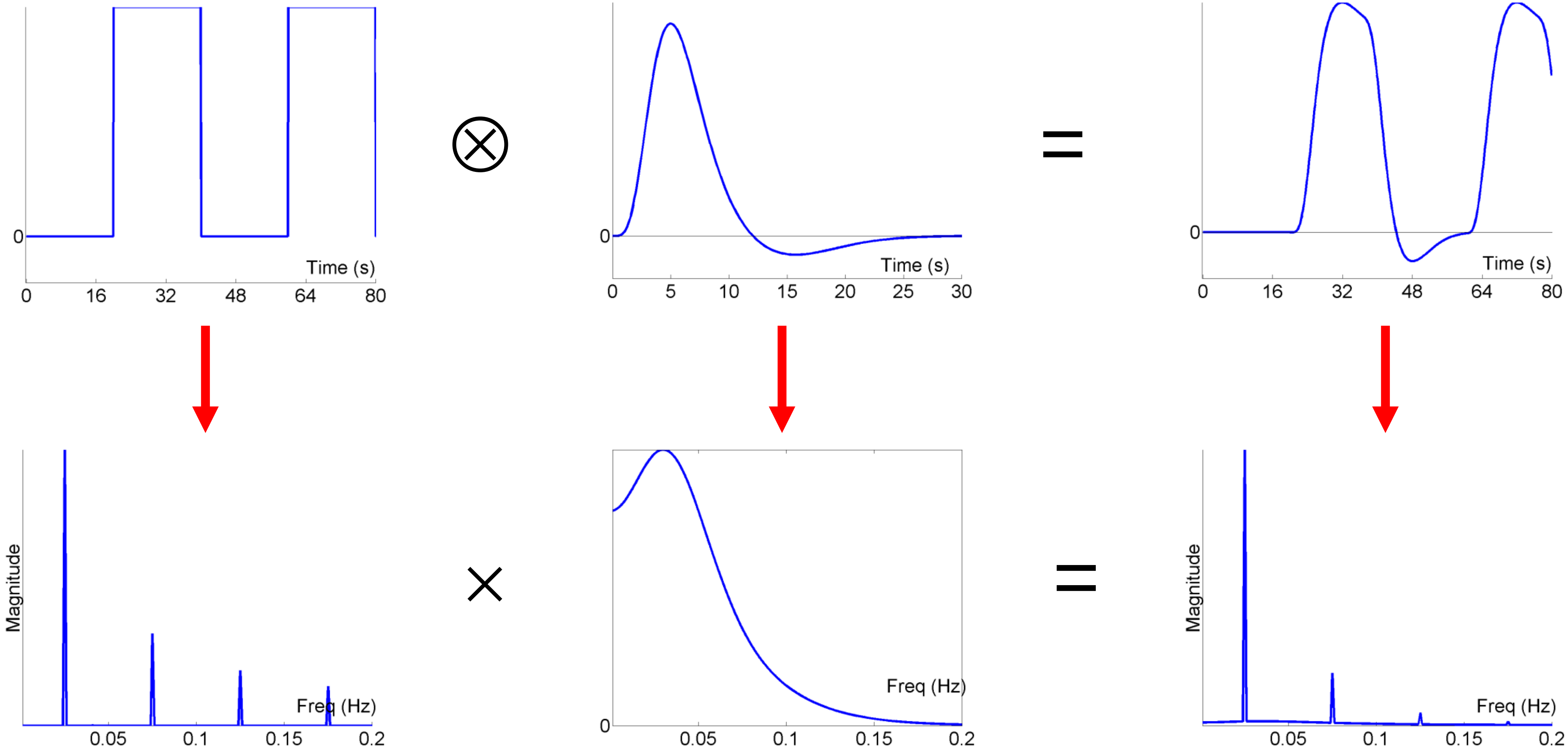
Animation: https://en.wikipedia.org/wiki/Fourier_transform

Blocked, epoch = 20s

Stimulus (“Neural”)

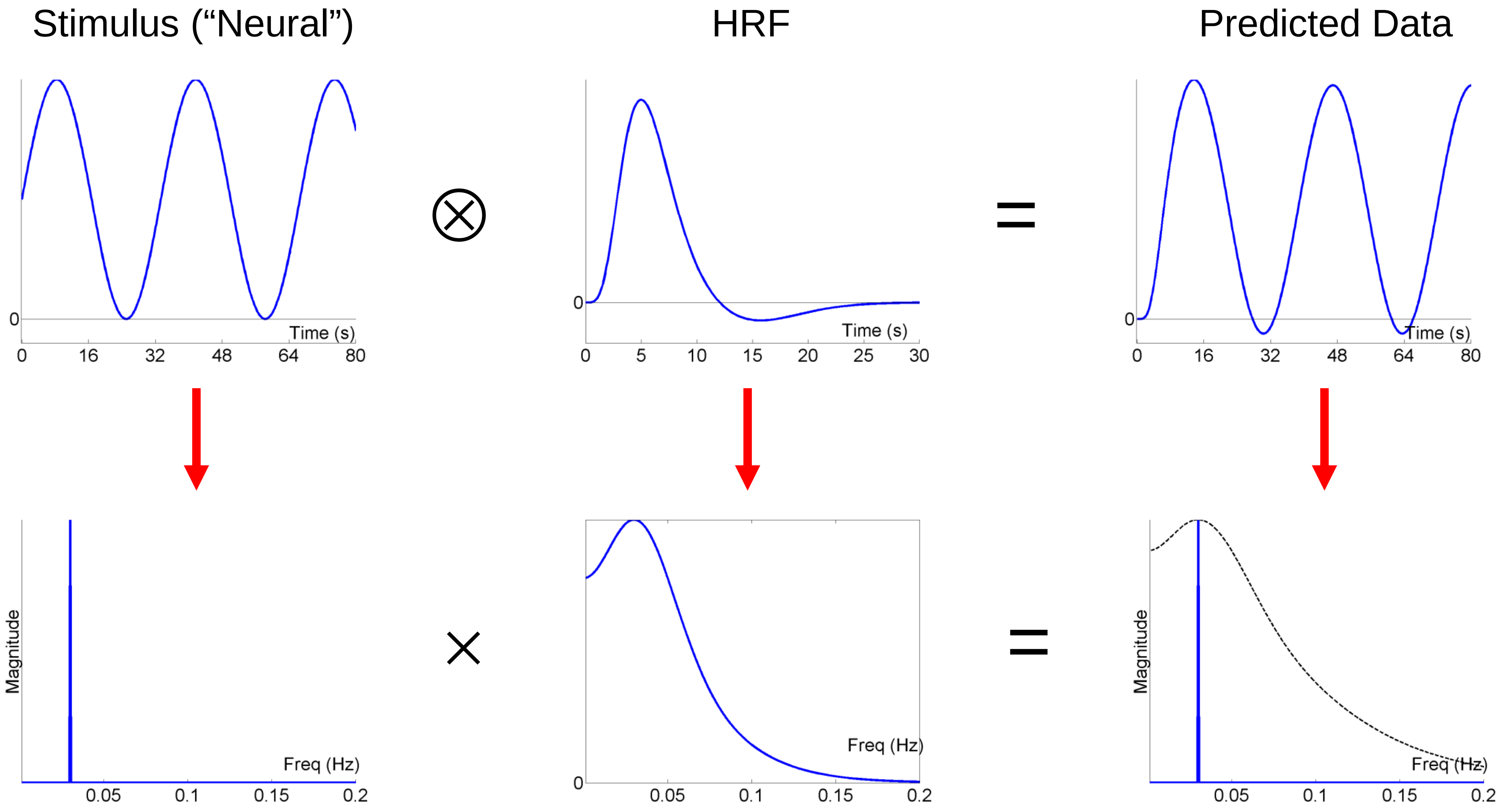
HRF

Predicted Data



Blocked-epoch (with short SOA)

Sinusoidal modulation, f = 1/33s



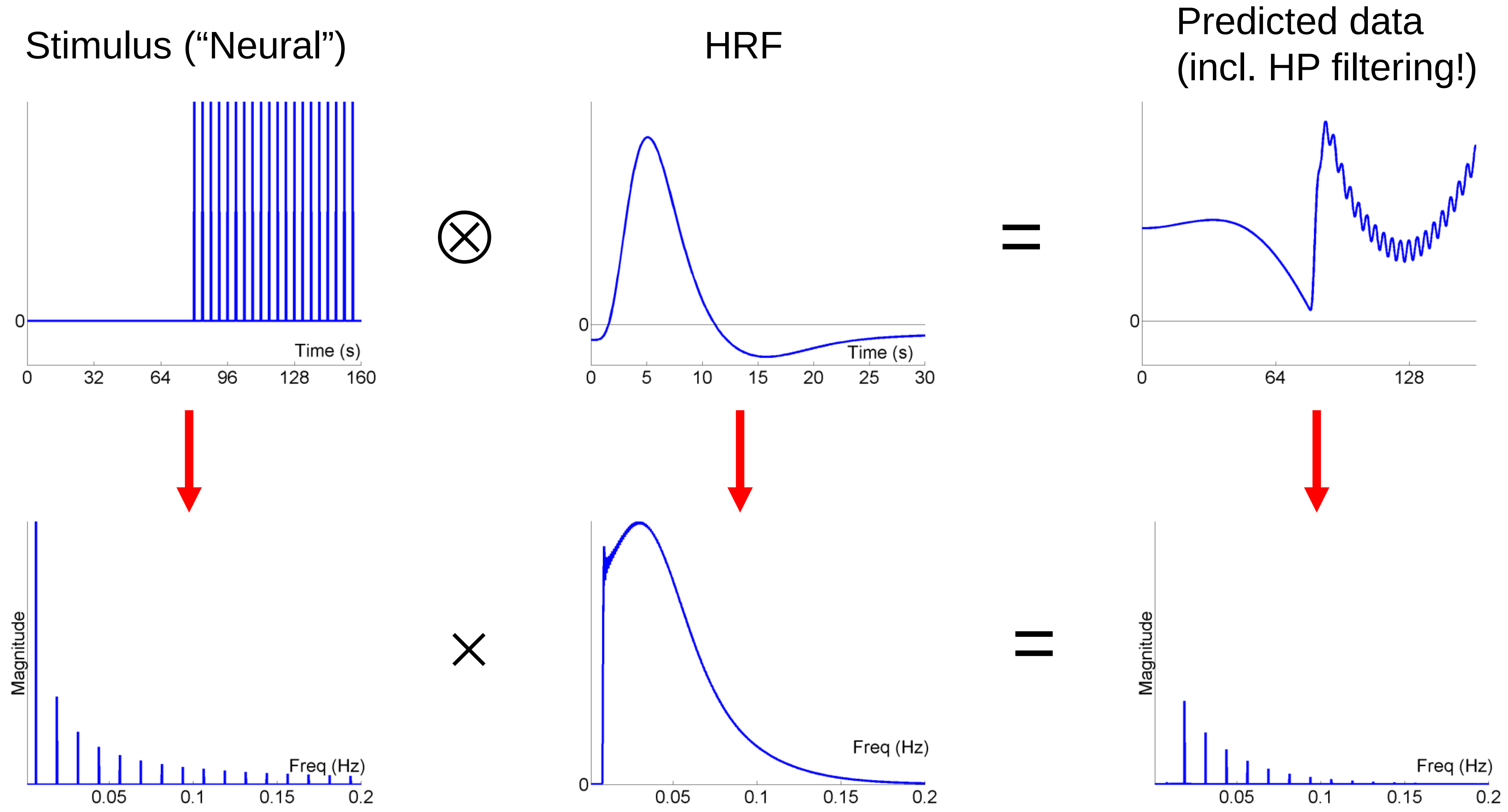
Stimulus (“Neural”)

HRF

Predicted Data

The most efficient design of all!

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

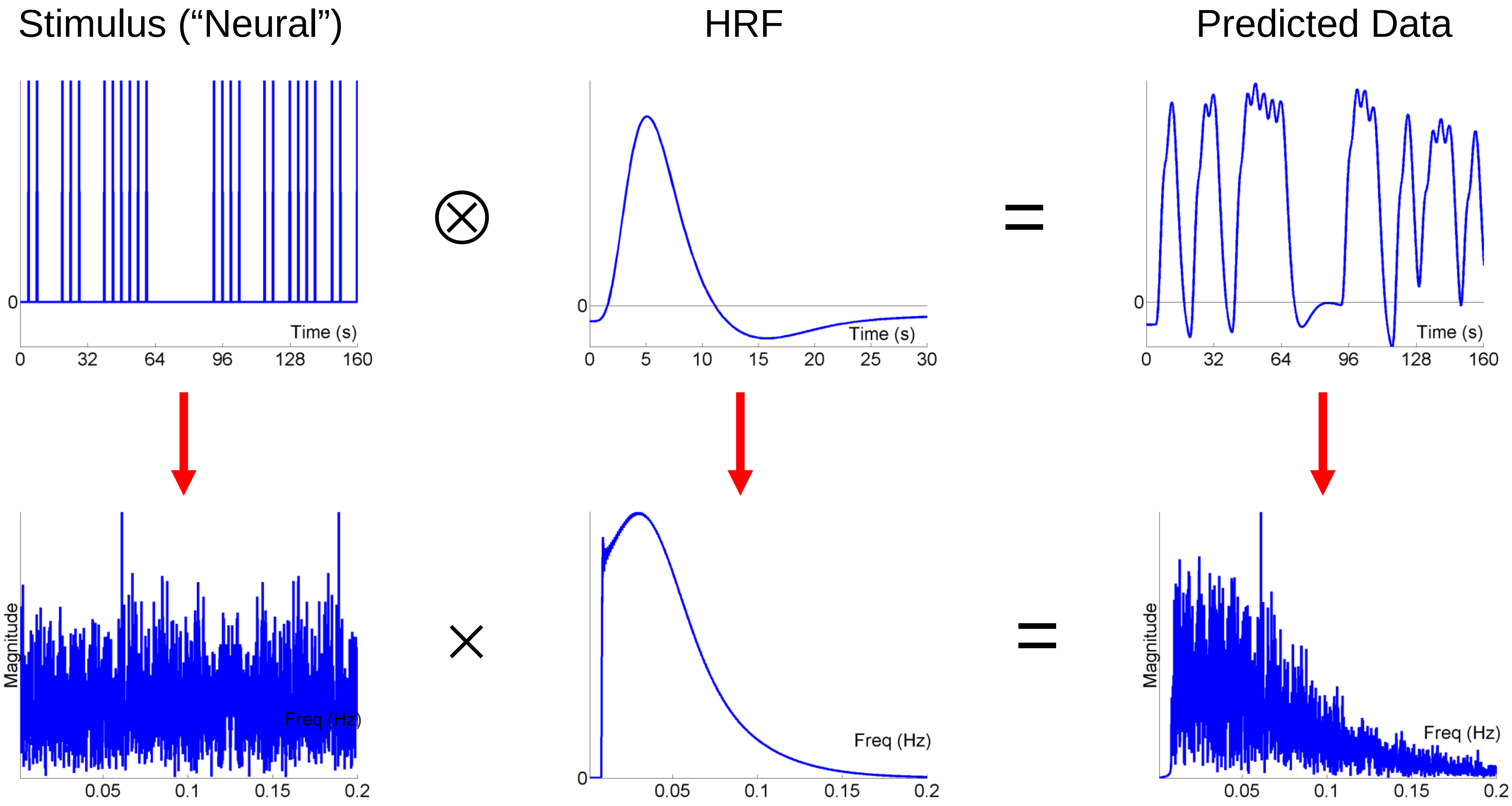

Stimulus (“Neural”)

HRF

Predicted data
(incl. HP filtering!)

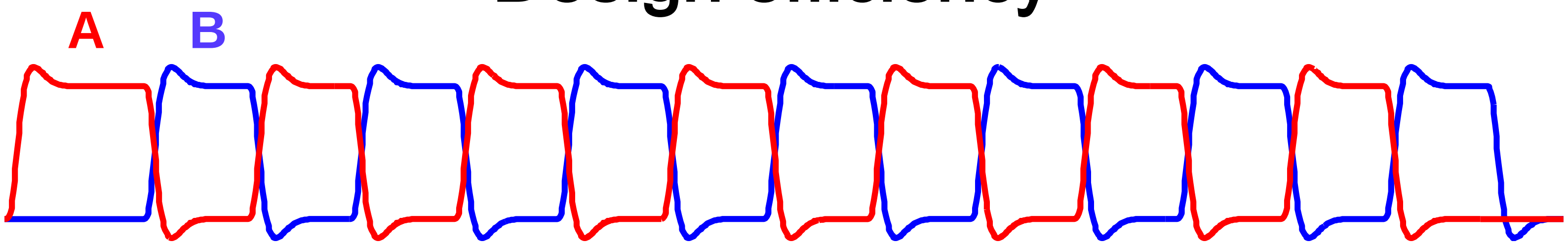
Don’t use long (>60s) blocks!

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



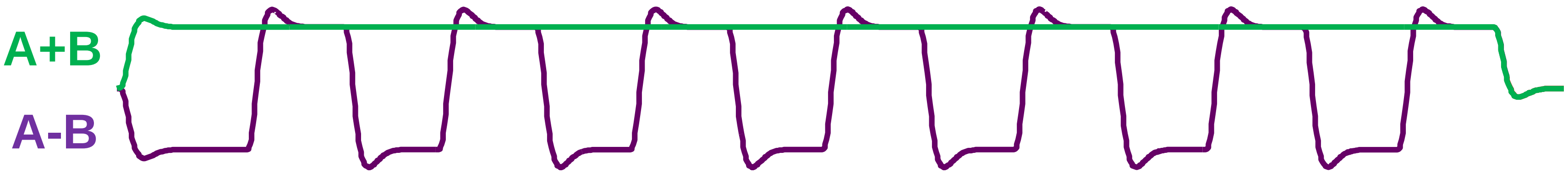
Randomised design spreads power over frequencies.

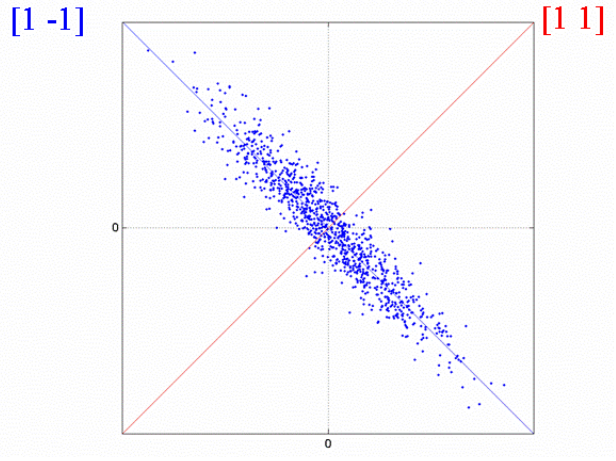
Design efficiency



$$X^T X = \begin{pmatrix} 1 & -0.9 \\ -0.9 & 1 \end{pmatrix}$$

$$c = [1\ 0]^T: \quad e(c, X) = 18.1$$
$$c = [0.5\ 0.5]^T: \quad e(c, X) = 19.0$$
$$c = [1\ -1]^T: \quad e(c, X) = 95.2$$





- ❑ High correlation between regressors leads to low sensitivity to each regressor alone.
- ❑ We can still estimate efficiently the difference between them.

Efficiency: Multiple event types

- Design parametrised by:

  SOA_{min} Minimum SOA

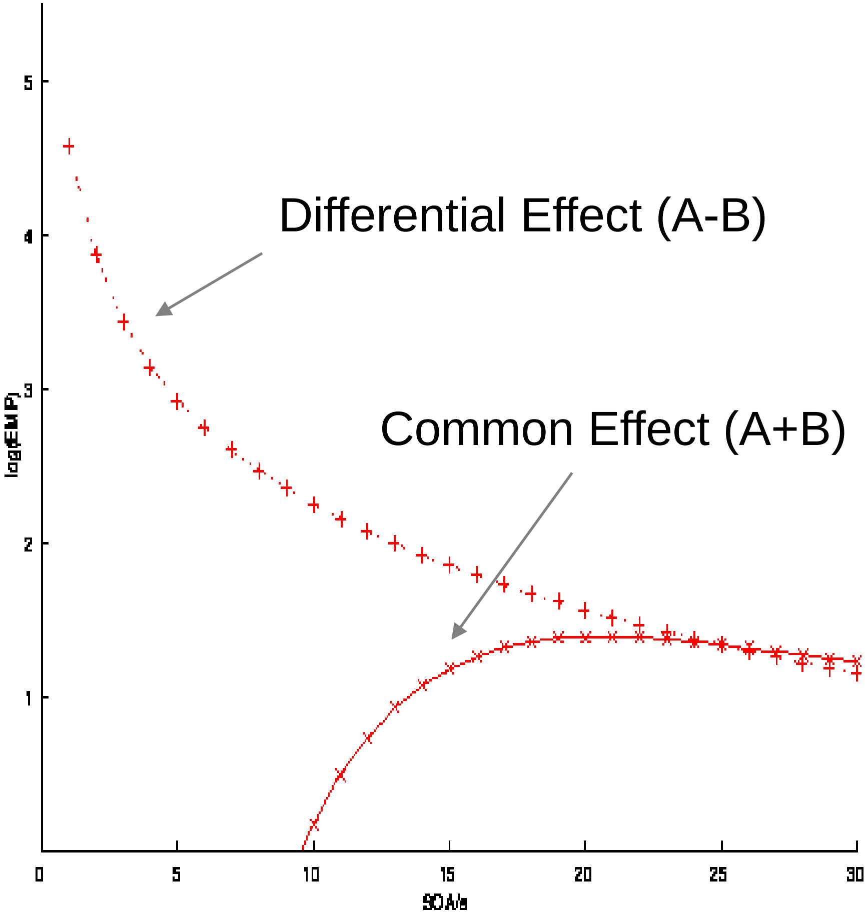
  $p_i(\mathbf{h})$ Probability of event-type i given history $\mathbf{h}$ of last m events

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

- Example: Randomised AB

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

=> **ABBBABAABABAAA...**



Differential Effect (A-B)

Common Effect (A+B)

4s smoothing; 1/60s highpass filtering

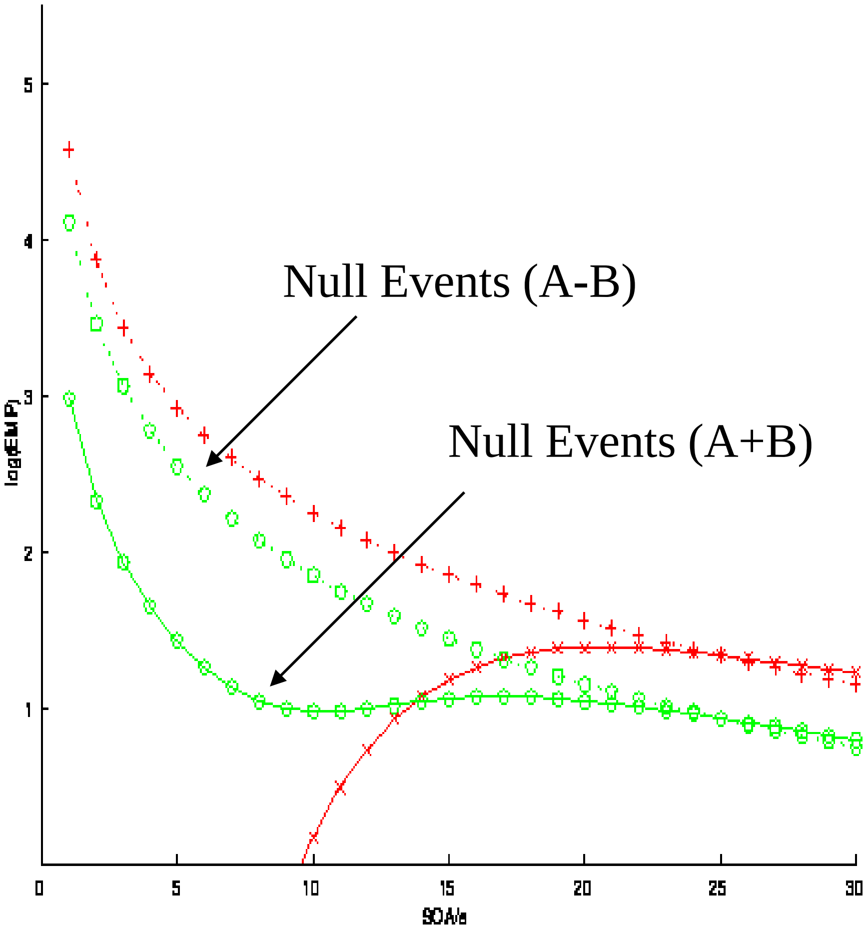
Efficiency: Multiple event types

- 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 corresponds to a third unmodelled event-type)



Null Events (A-B)

Null Events (A+B)

4s smoothing; 1/60s highpass filtering

Efficiency – main conclusions

- Optimal design for one contrast may not be optimal for another.

- Generally, blocked designs with short SOAs are the most efficient design.

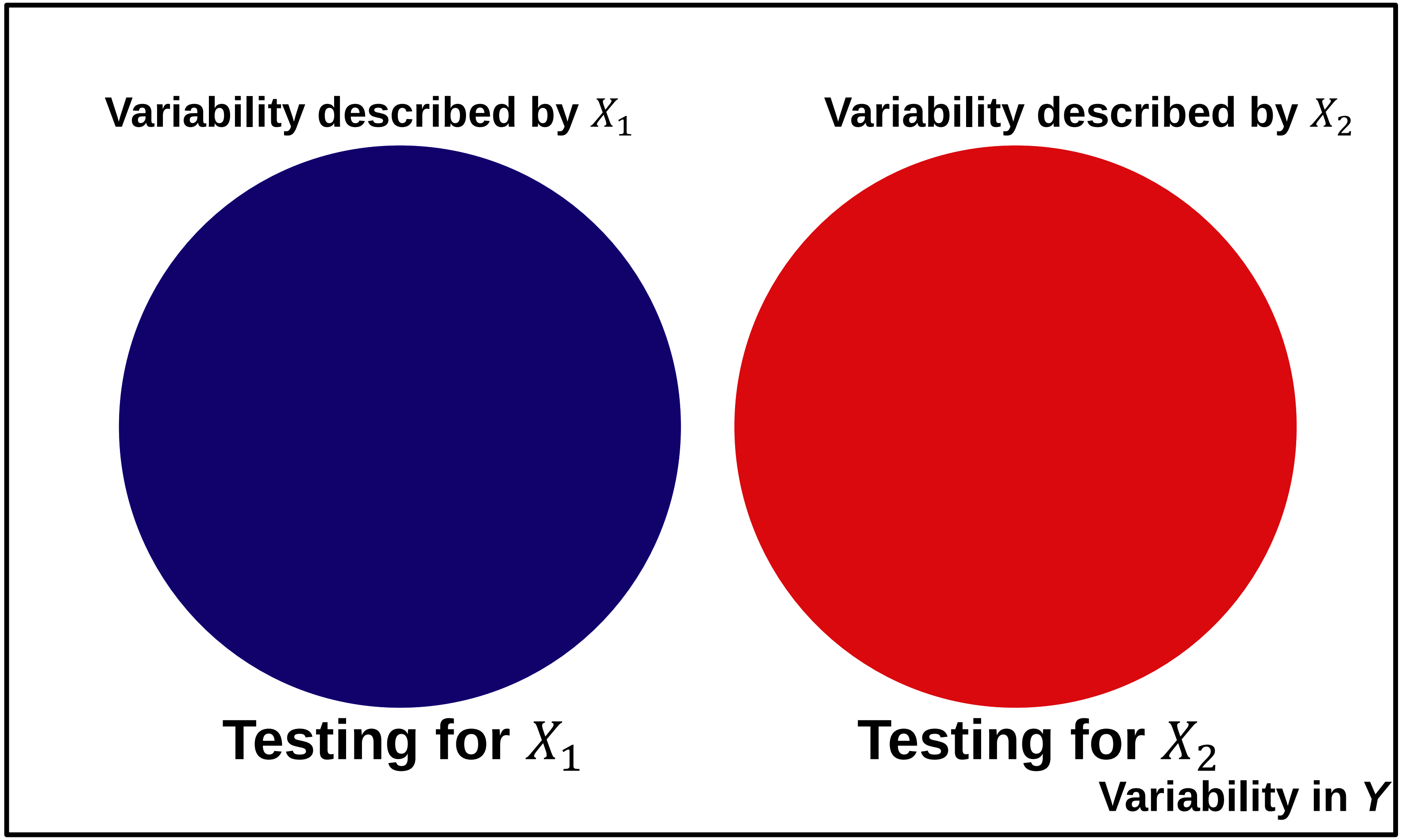
- With randomised designs, optimal SOA for differential effect (A-B) is minimal SOA (assuming no saturation), whereas optimal SOA for common effect (A+B) is 16-20s.

- Inclusion of null events gives good efficiency for both common and differential effects at short SOAs.

Appendix: Orthogonal regressors

What's (not) the problem if I use a design with correlated regressors?

Orthogonal regressors



Variability described by X_1

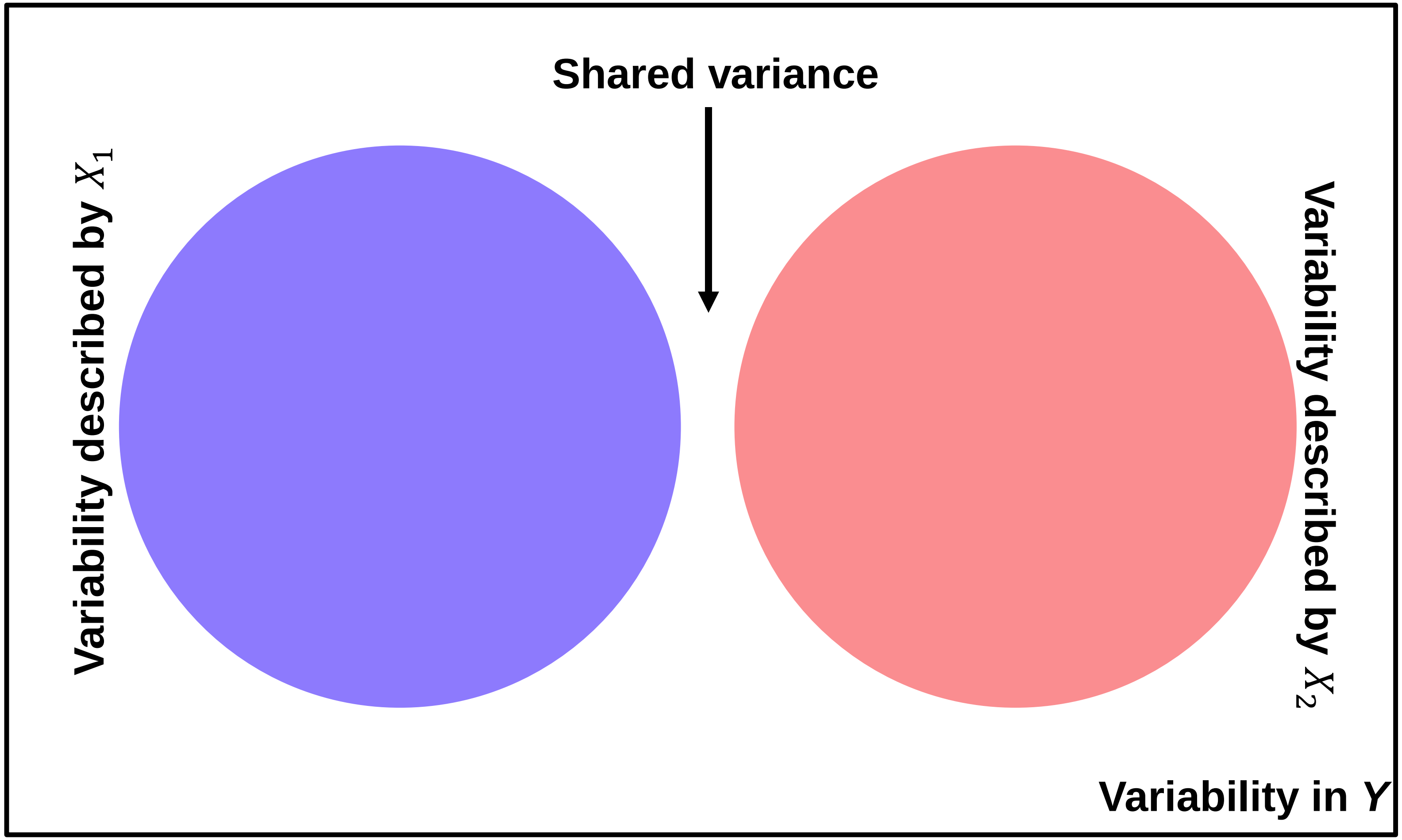
Variability described by X_2

Testing for X_1

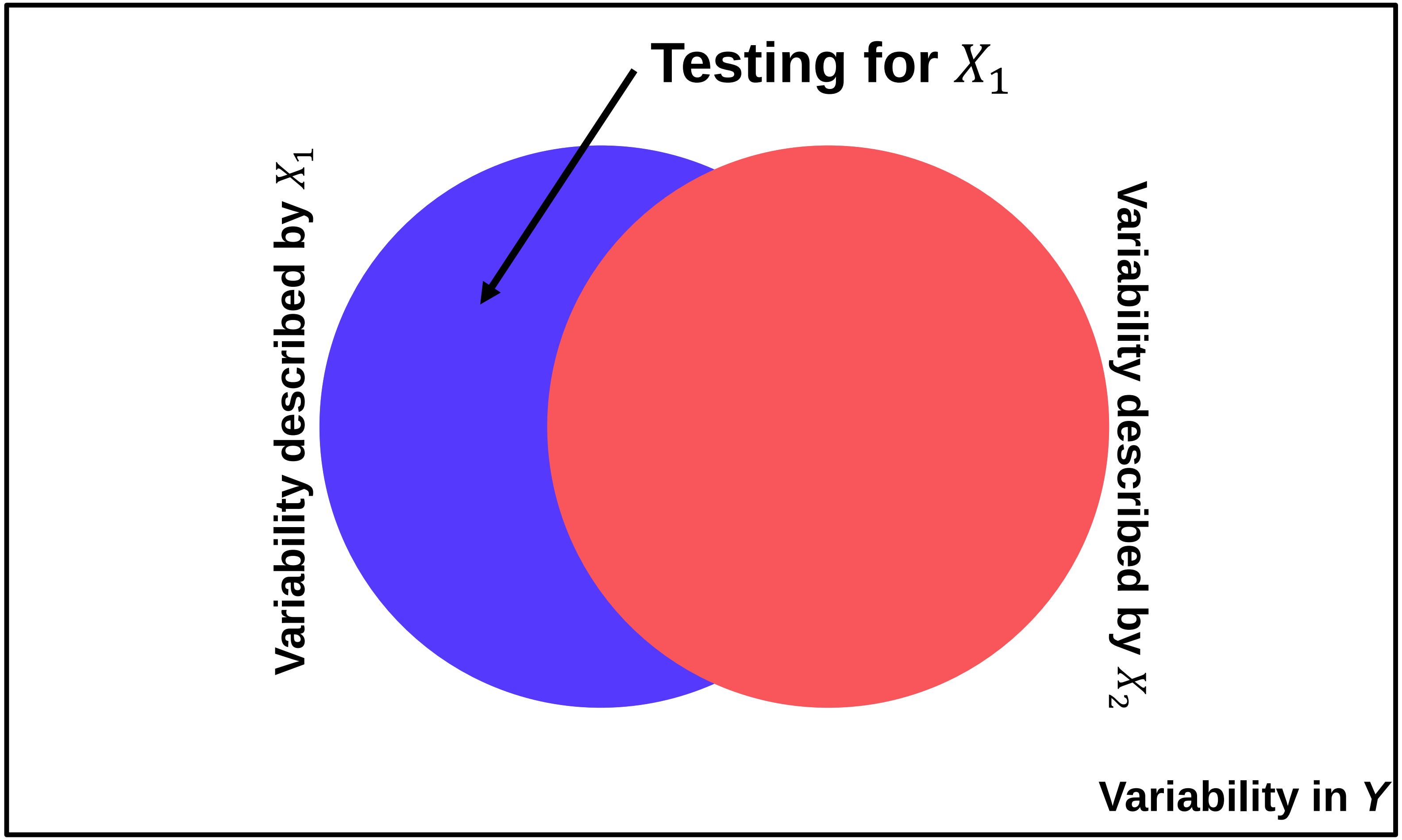
Testing for X_2

Variability in *Y*

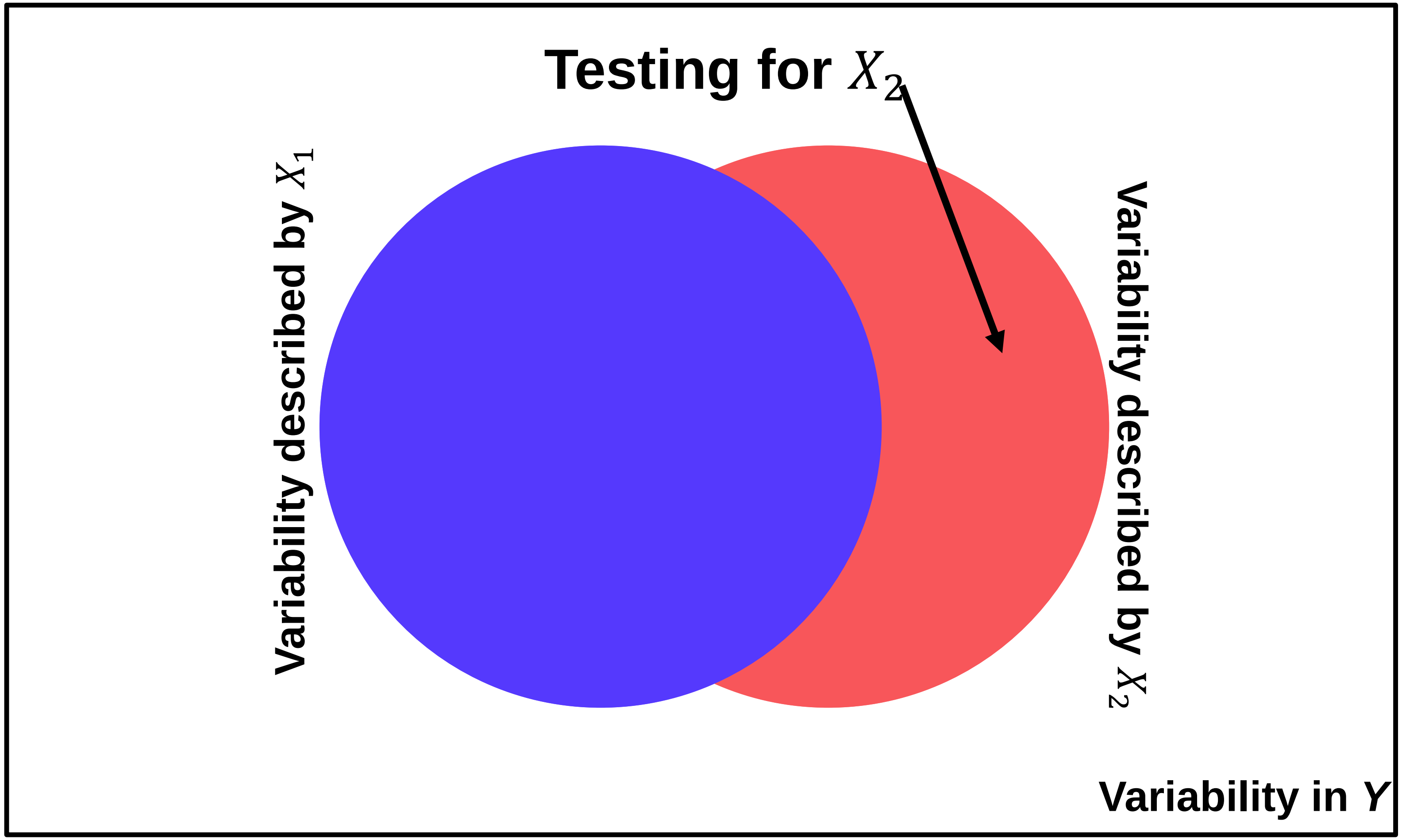
Correlated regressors



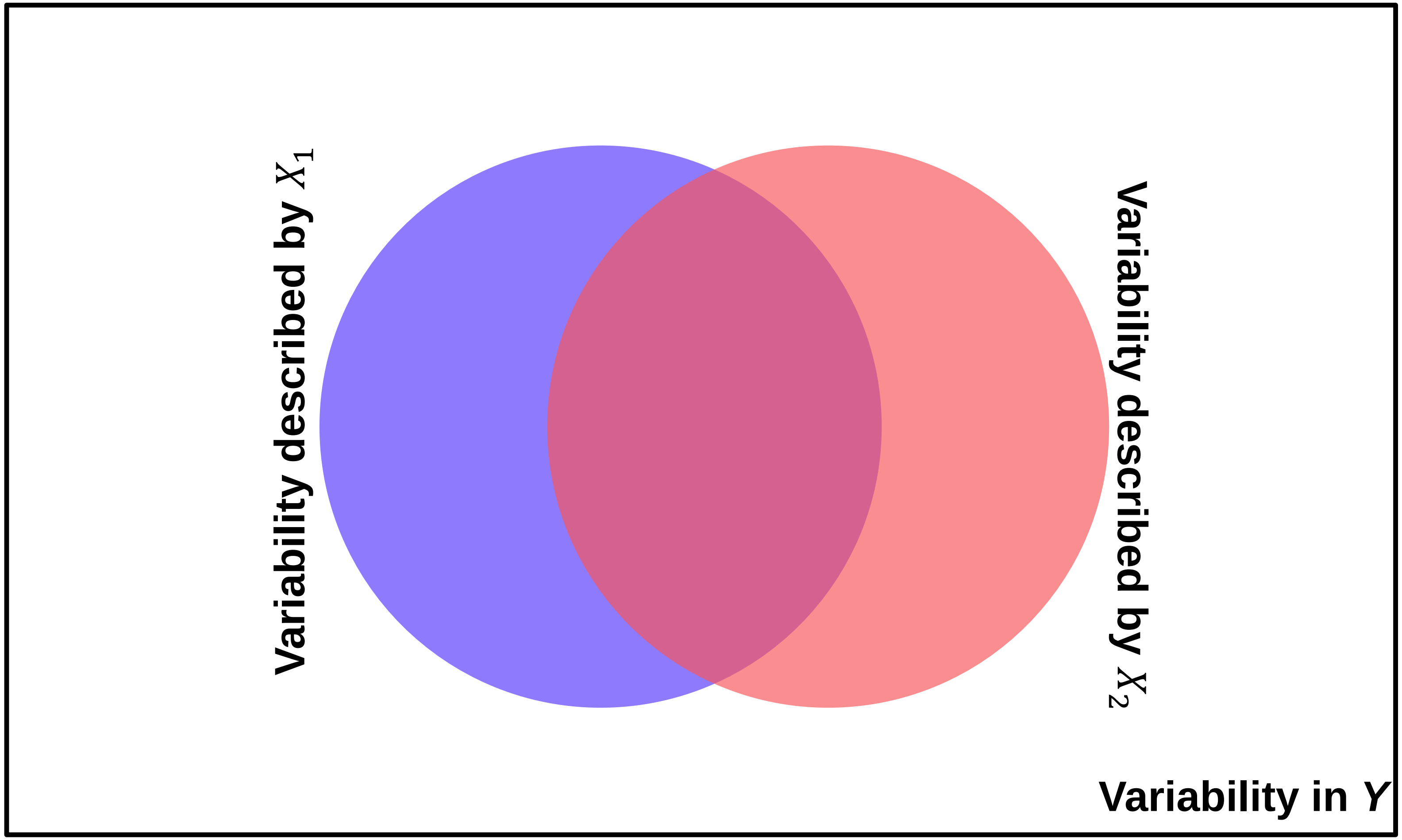
Correlated regressors



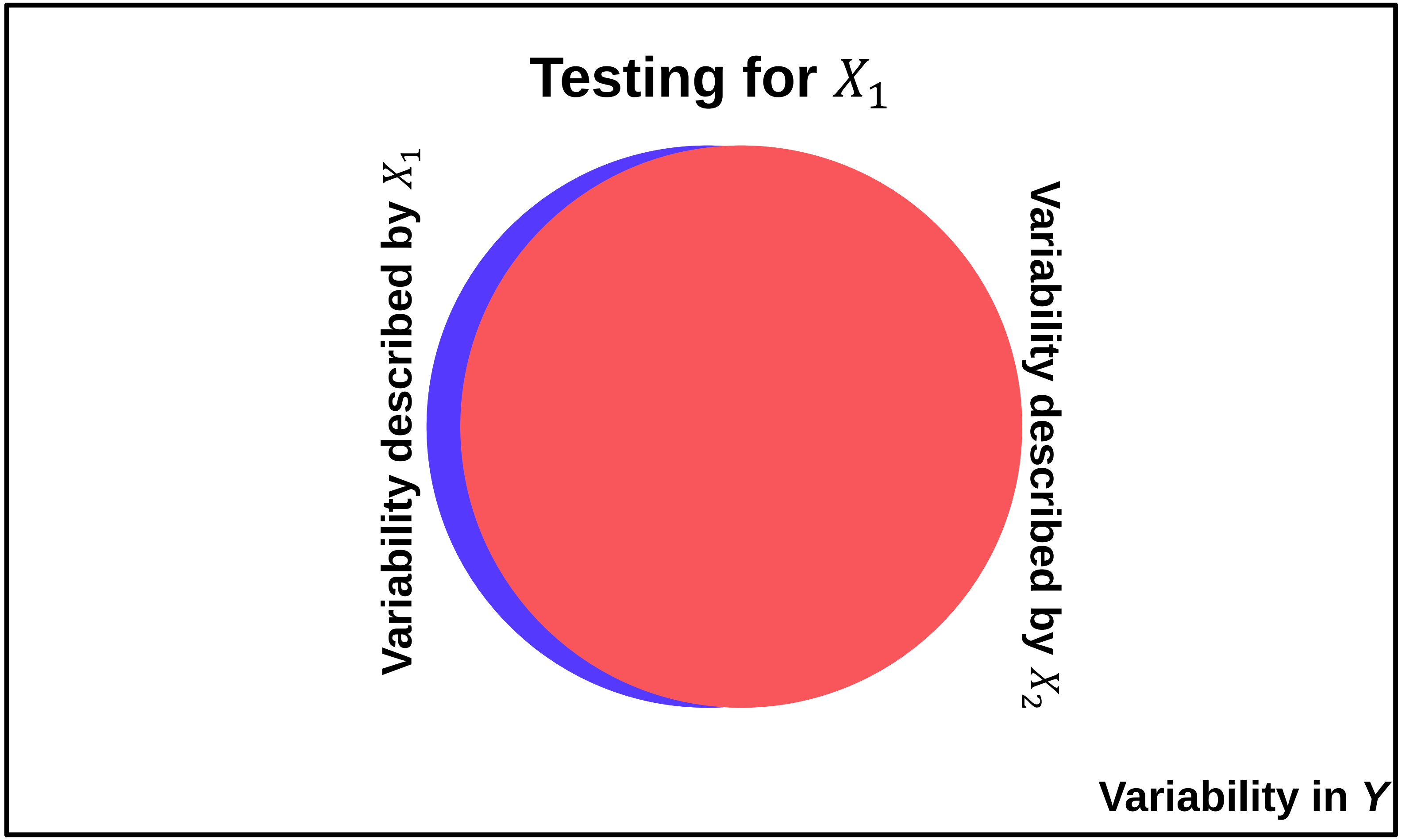
Correlated regressors



Correlated regressors



Correlated regressors



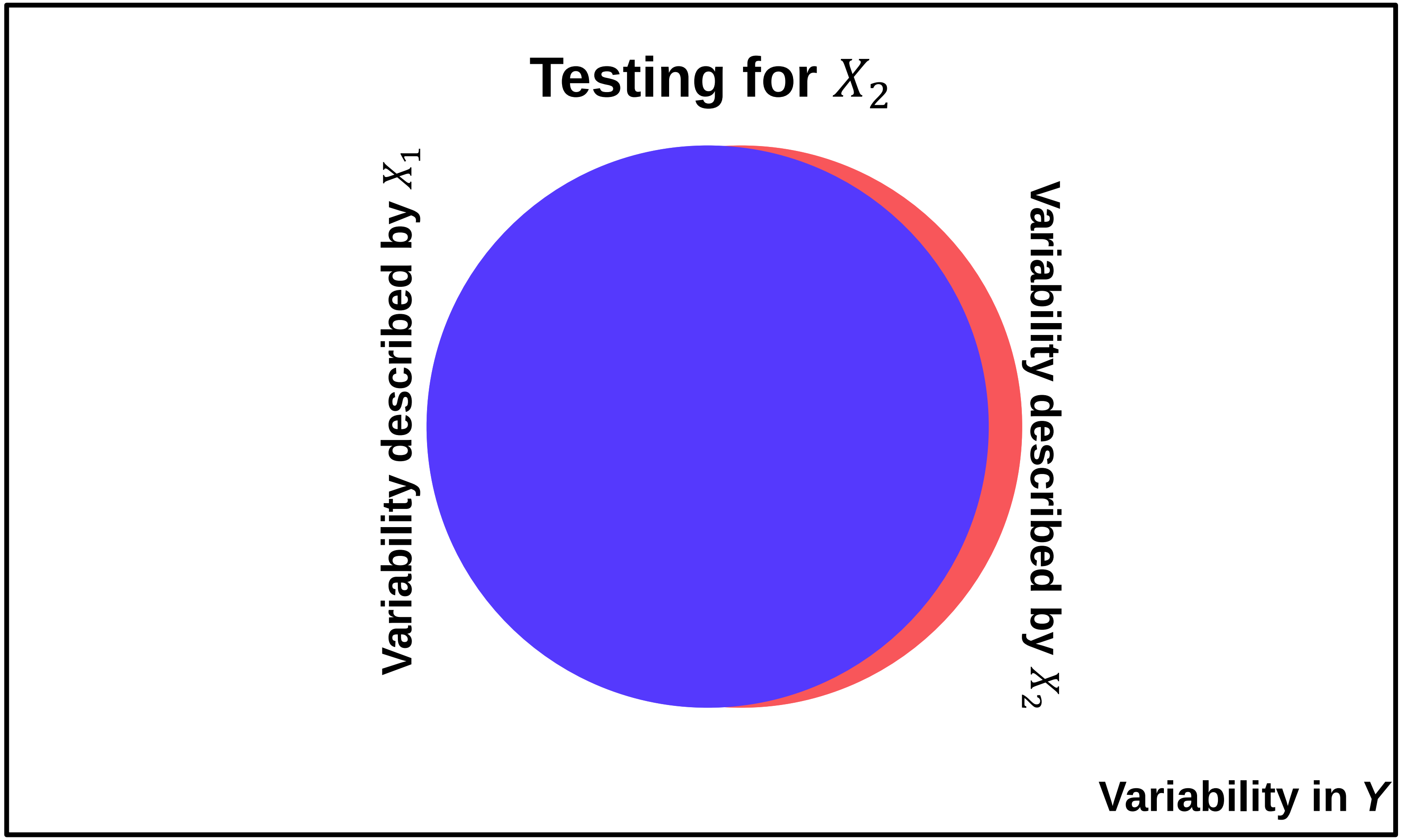
Testing for X_1

Variability described by X_1

Variability described by X_2

Variability in Y

Correlated regressors



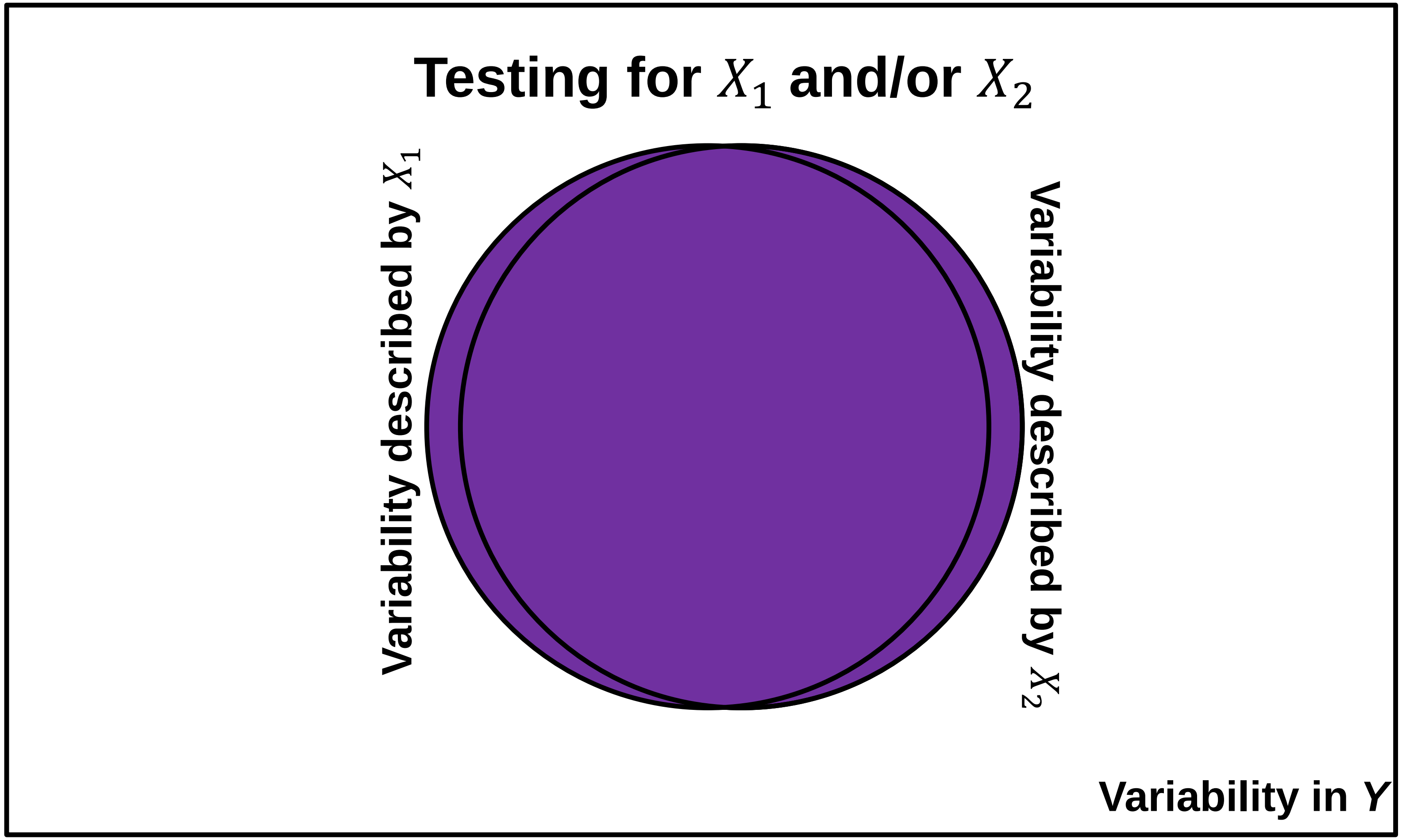
Testing for X_2

Variability described by X_1

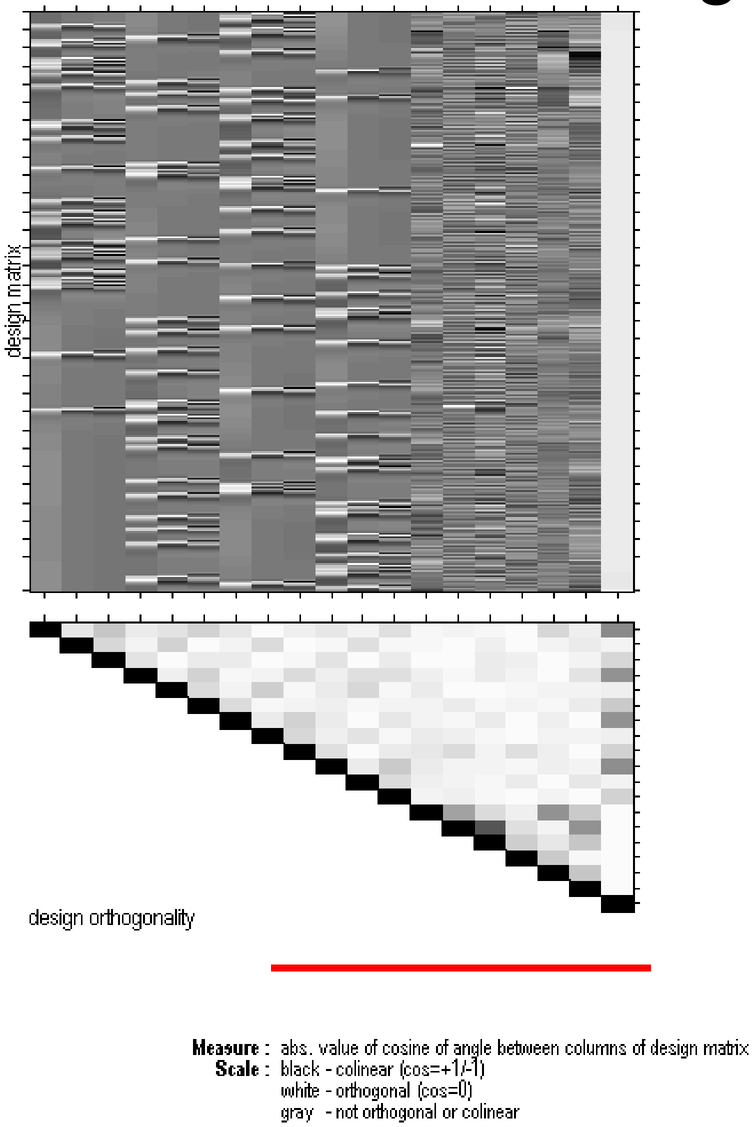
Variability described by X_2

Variability in Y

Correlated regressors



Design orthogonality



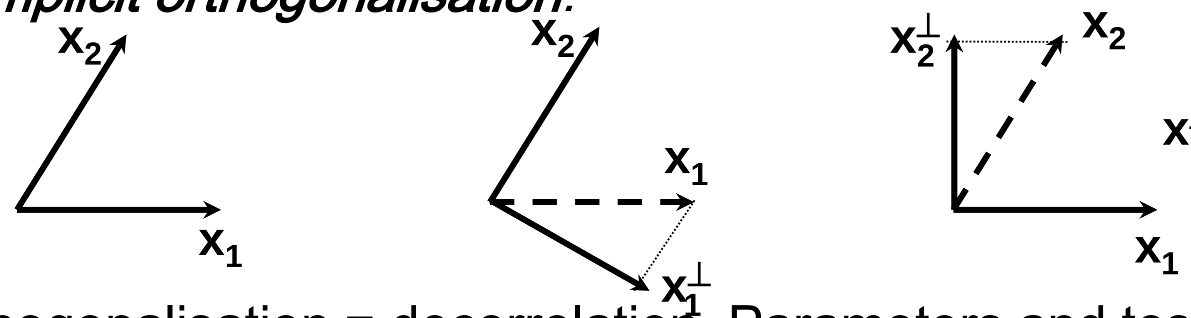
Measure : abs. value of cosine of angle between columns of design matrix
Scale : black - colinear (cos=+1/-1)
white - orthogonal (cos=0)
gray - not orthogonal or colinear

For each pair of columns of the design matrix, the orthogonality matrix depicts the magnitude of the **cosine of the angle** between them, with the range 0 to 1 mapped from white to black.

- **If both vectors have zero mean then the cosine of the angle between the vectors is the same as the correlation between the two variates.**

Correlated regressors: summary

- We implicitly test for an **additional** effect only. When testing for the first regressor, we are effectively removing the part of the signal that can be accounted for by the second regressor:
  ⇨ *implicit orthogonalisation.*



$$x_2^\perp = x_2 - x_1.x_2\ x_1$$

- Orthogonalisation = decorrelation. Parameters and test on the non modified regressor change.
  Rarely solves the problem as it requires assumptions about which regressor to uniquely attribute the common variance.
  ⇨ change regressors (i.e. design) instead, e.g. factorial designs.
  ⇨ use F-tests to assess overall significance.
- Original regressors may not matter: it’s the contrast you are testing which should be as decorrelated as possible from the rest of the design matrix

Thank you