Advanced designs
Advanced Analysis: Parametric Designs

Scenario:
Interested in specific responses to multiple levels of a painful stimulus

Specific questions:
Are there regions showing significant responses to painful stimuli?
Are there regions where higher intensity stimuli produce larger responses?
Are there regions with a linear response across multiple levels of stimuli?

Solution:
Multiple regressors
Contrasts and F-tests
Analysis of responses to multiple levels of painful stimuli: modelling

- Possible approach: model a specific hypothesis - high produces twice the response as low
- Pre-supposes relationship between stimulation strength and response
- Can only ask the question about the pre-supposed relationship
Analysis of responses to multiple levels of painful stimuli: modelling

- Better approach: model as if two completely different stimuli
- Now, no pre-supposition about relationship between stimulation strength and response
- Can assess responses to individual stimuli
  - \( t\)-contrast \([0 1]\): “response to low pain”
Analysis of responses to multiple levels of painful stimuli: modelling

- Better approach: model as if two completely different stimuli
- Now, no pre-supposition about relationship between stimulation strength and response

- Can compare the size of the fits of the two regressors -
  - t-contrast [1 -1] : "is the response to high pain greater than that to low pain ?"
  - t-contrast [-1 1] : "is the response to low pain greater than that to high pain ?"
Analysis of responses to multiple levels of painful stimuli: modelling

- Better approach: model as if two completely different stimuli
- Now, no pre-supposition about relationship between stimulation strength and response

- Average response?
  - t-contrast \([1\ 1]\) : "is the average response to pain greater than zero?"
Parametric Variation: Linear Trends

- Is there a linear trend between the BOLD response and stimulus intensity?
Parametric Variation: Linear Trends

• Is there a linear trend between the BOLD response and stimulus intensity?
A three-strength experiment

Is there a linear trend between the BOLD response and some task variable?

t-contrast [-1 0 1] : Linear trend
Parametric Variation: Linear Trends

- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- t-contrast [-1 0 1] : Linear trend
A three-strength experiment

Is there a linear trend between the BOLD response and some task variable?

t-contrast \([-1 0 1]\) : Linear trend

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Linear</th>
<th>1</th>
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<tbody>
<tr>
<td>low c1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>medium c2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>high c3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>+ linear c4</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>- linear c5</td>
<td>1</td>
<td>-1</td>
</tr>
</tbody>
</table>
Parametric Variation: Linear Trends

- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- $t$-contrast $[-1 \ 0 \ 1]$: Linear trend
Parametric Variation: Linear Trends

- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- $t$-contrast $[-1 \ 0 \ 1]$: Linear trend

Slope ($\beta_3 - \beta_1$) is the same for both...
Parametric Variation: Linear Trends

- A four-strength experiment
- t-contrast [-3 -1 1 3] : Positive linear trend

<table>
<thead>
<tr>
<th>C1</th>
<th>strength 1</th>
<th>1</th>
<th>0</th>
<th>0</th>
<th>0</th>
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<tbody>
<tr>
<td>C2</td>
<td>strength 2</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>C3</td>
<td>strength 3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>C4</td>
<td>strength 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C5</td>
<td>pos trend</td>
<td>-3</td>
<td>-1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>C6</td>
<td>neg trend</td>
<td>3</td>
<td>1</td>
<td>-1</td>
<td>-3</td>
</tr>
</tbody>
</table>
Parametric Variation: Linear Trends

- A four-strength experiment
- t-contrast \([-3 \ -1 \ 1 \ 3]\): Positive linear trend

<table>
<thead>
<tr>
<th></th>
<th>strength 1</th>
<th>strength 2</th>
<th>strength 3</th>
<th>strength 4</th>
<th>pos trend</th>
<th>neg trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C2</td>
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<td>1</td>
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<td>0</td>
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</tr>
<tr>
<td>C3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C5</td>
<td>-3</td>
<td>-1</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C6</td>
<td>3</td>
<td>1</td>
<td>-1</td>
<td>-3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\[-3 \ -1 \ 1 \ 3\]

\[-2 \ -1 \ 1 \ 2\]
But what if it isn’t that predictable?

Auditory word presentation at different rates
But what if it isn’t that predictable?

Auditory word presentation at different rates

Bonkers!

True story
But what if it isn’t that predictable?

Given this design what would be “reasonable” questions to ask?

More activation to 500 than to 100 WPM?

But no...
But what if it isn’t that predictable?

Given this design what would be “reasonable” questions to ask?

Activation proportional to WPM?

Still no...
But what if it isn’t that predictable?

Given this design what would be “reasonable” questions to ask?

Inversely proportional to WPM squared?

Yaay!

True story
But what if it isn’t that predictable?

Given this design what would be “reasonable” questions to ask?

Inversely proportional to WPM squared?

But seriously ... would you have asked that question?

Yaay!

True story
But what if it isn’t that predictable?

There is a (very real) risk of missing interesting but unpredicted responses

What can we do about that?
F-contrasts to the rescue

We can define an F-contrast that spans “the range of possible responses”

An F-contrast is a series of questions (t-contrasts) with an OR between them
F-contrasts to the rescue

We can define an F-contrast that spans “the range of possible responses”

Let’s start with “Greater activation to 200 than 100 WPM”
F-contrasts to the rescue

We can define an F-contrast that spans “the range of possible responses”

OR

300WPM > 200WPM
F-contrasts to the rescue

We can define an F-contrast that spans “the range of possible responses”

OR

400WPM > 300WPM
F-contrasts to the rescue

OR

500 WPM > 400 WPM

N.B.
F-contrasts to the rescue

But ... that doesn’t span all possible response, what about for example 300>100?
F-contrasts to the rescue

But ... that doesn’t span all possible response, what about for example 300>100?

300>100 implies 200>100 AND/OR 300>200 which we have covered
F-contrasts to the rescue

But ... what about for example 100>200, you haven’t covered that?

This t-contrast asks “where is 200>100?”

F-contrasts are bi-directional
F-contrasts to the rescue

But ... what about for example 100>200, you haven’t covered that?

But this F-contrast asks “where is 200≠100?”

F-contrasts are bi-directional
Advanced Analysis: Parametric Designs

Summary:

• Important to have separate EVs (and parameters) per level of stimulus, otherwise assuming an exact linear response

• Linear trends require contrasts that are centred about zero and with even intervals

• Going beyond linear trends can be done with F-tests to look for arbitrary response shapes
Advanced Analysis:
Factorial Designs and Interactions

Scenario:
Investigating in multi-sensory regions

Specific questions:
What regions show responses to vision, touch
What regions respond significantly to both?
Are responses additive where there is both visual and touch stimulation, or is there an interaction?

Solution:
Specific regressors
Contrast masking
Multisensory study

- EV1 models vision on/off
- EV2 models touch on/off

- Can generate simple contrasts for:
  - vision activation/deactivation \([ 1 \ 0 ]\)
  - touch activation/deactivation \([ 0 \ 1 ]\)
  - differences in responses \([ 1 \ -1 ]\)

- Regions showing both visual and tactile response??
- Not \([ 1 \ 1 ]\): this only assesses the average
Contrast Masking

- Often it is of interest to identify regions showing significant effects in multiple contrasts (e.g. responds to visual AND tactile stimulations)
- This can be achieved by masking a thresholded z image for a chosen contrast using the thresholded z image from one or more other contrasts.
Contrast Masking

- Often it is of interest to identify regions showing significant effects in multiple contrasts (e.g. responds to visual AND tactile stimulations)
- This can be achieved by masking a thresholded z image for a chosen contrast using the thresholded z image from one or more other contrasts.

For example, say we had two t contrasts C1 (1 0) and C2 (0 1). We may be interested in only those voxels which are significantly "active" for both contrasts.
Contrast Masking

• Rather than masking with voxels which survive thresholding, it may be desirable to mask using positive z statistic voxels instead.

For example, say that we have two t contrasts C3 (1 -1) and C1 (1 0). It may be desirable to see those voxels for which EV1 is bigger than EV2, only when EV1 is positive.
Factorial design

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Allows you to characterise interactions between component processes
  - i.e. effect that one component has on another
No Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing Vision and Touch comparison](image)
### No Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
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</tbody>
</table>

![Graph](image)

- Vision
- Touch
- Vision + Touch
No Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
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</tbody>
</table>

No interaction - effects add linearly
Positive Interaction
Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Touch</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Touch</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing Vision, Touch, and Vision+Touch effects](image)

- Vision
- Touch
- Vision+Touch
Positive Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
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</tbody>
</table>

Positive interaction - “superadditive”
### Negative Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
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</tbody>
</table>

![Bar chart showing Vision, Touch, and Vision+Touch effects]
## Negative Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
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</tbody>
</table>

Negative interaction - “subadditive”

![Graph showing the comparison of Vision, Touch, and Vision+Touch effects.](image-url)
Modelling Interactions Between EVs

- EV1 models vision on/off
- EV2 models touch on/off

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
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</tbody>
</table>
Modelling Interactions Between EVs

- EV1 models vision on/off
- EV2 models touch on/off
- EV3 Models interaction

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

```
C1  vision      1   0   0
C2  touch       0   1   0
C3  Pos interaction 0   0   1
C4  Neg interaction 0   0  -1
```
Advanced Analysis: Factorial Designs and Interactions

Summary:

• Contrast masking allows questions of the form “A and B” to be asked
  • F-tests ask “A or B or both”

• Factorial design covers different combinations including the interaction

• Interaction can be positive, negative or none and is tested using an extra EV and a simple contrast
Advanced Analysis: Correlation of EVs and Design Efficiency
Correlation of EVs

- Correlated EVs are relatively common, but strong correlation is a problem in either first-level or group-level designs.

- When EVs are correlated, it is the unique contribution from each EV that determines the model’s fit to the data and the statistics.

- Start by looking at first-level examples:
  - correlation and rank deficiency
  - design efficiency tool
Correlation of EVs: First-level designs
Design Matrix Rank Deficiency

- A design matrix is rank deficient when a linear combination of EVs is exactly zero
  - Model can fit exactly the same signal in multiple ways!
  - e.g. visual and tactile stimulation occurs at very similar times, so it is not possible to separate the responses!
Design Matrix Rank Deficiency

- A design matrix is rank deficient when a linear combination of EVs is exactly zero
- Model can fit exactly the same signal in multiple ways!
- e.g. visual and tactile stimulations are exactly opposed (so no baseline)
Design Matrix Rank Deficiency

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An example experiment
An FMRI adaptation of a classical PET experiment

• Three types of events
• 1st type: Word Generation
• 2nd type: Word Shadowing
• 3rd type: Null event
• 6 sec ISI, random order
Design Matrix Rank Deficiency

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An example experiment

An FMRI adaptation of a classical PET experiment

- Three types of events
  - 1st type: Word Generation
  - 2nd type: Word Shadowing
  - 3rd type: Null event
- 6 sec ISI, random order

Generation

Shadowing

445 seconds
A design matrix is rank deficient when a linear combination of EVs is exactly zero.

- Model can fit exactly the same signal in multiple ways!
- E.g. visual and tactile stimulations are exactly opposed (so no baseline)
Design Matrix Rank Deficiency

• A design matrix is rank deficient when a linear combination of EVs is exactly zero
• Model can fit exactly the same signal in multiple ways!
• e.g. modelling visual, tactile, and rest (the last one is effectively baseline and shouldn’t be modelled in FSL)
Close to Rank Deficient Design Matrices

- **Good News:** The statistics always take care of being close to rank deficient
Close to Rank Deficient Design Matrices

• **Good News:** The statistics always take care of being close to rank deficient

• **Bad News:** the ignorant experimenter may have found no significant effect, because:
  a) Effect size was too small.
  b) Being close to rank deficient meant finding an effect would have required a HUGE effect size
     e.g. may need a lot of data to determine how two EVs with very similar timings best combine to explain the data.
When do we have a problem?

• Depends on SNR, and **crucially** the contrasts we are interested in:
  
  • \([1 \ -1]\) e.g. vis-tact??
  
  • \([1 \ 1]\) e.g. average response??
  
  • \([1 \ 0]\) or \([0 \ 1]\) ?? e.g. visual? or tactile?
When do we have a problem?

• Depends on SNR, and **crucially** the contrasts we are interested in:
  
  • \([1 \ -1]\) e.g. vis-tact??  
    - no problem
  
  • \([1 \ 1]\) e.g. average response??  
    - no chance
  
  • \([1 \ 0]\) or \([0 \ 1]\) ?? e.g. visual? or tactile?  
    - no chance
When do we have a problem?

- Depends on SNR, and **crucially** the contrasts we are interested in:

  - $[1 \ 0]$: EV1 only (i.e. Generation vs rest)
  - $[0 \ 1]$: EV2 only (i.e. Shadowing vs rest)
  - $[1 \ 1]$: EV1 + EV2 (Mean activation)
  - $[-1 \ 1]$: EV2 - EV1 (More activated by Shadowing than Generation)
  - $[1 \ -1]$: EV1 - EV2 (More activated by Generation than Shadowing ($t$-tests are directional))

If we had not had the null events...
Design Efficiency

$t$-contrasts

$\begin{bmatrix} 1 & 0 \end{bmatrix}$

The Model & the Contrast
and the Residual Error

Remember this?
Design Efficiency

Analysis of responses to multiple levels of painful stimuli: modelling

- Possible approach: model a specific hypothesis - high produces twice the response as low
- Pre-supposes relationship between stimulation strength and response
- Can only ask the question about the pre-supposed relationship

And this?

Remember this?
The Model & the Contrast and the Residual Error
Design Efficiency

Tools of classical inference

1. A null-hypothesis
2. A test-statistic

Or expressed in GLM lingo

\[
\begin{bmatrix}
\hat{\beta}_1 \\
\hat{\beta}_2
\end{bmatrix} = \begin{bmatrix}
\beta_1 \\
\beta_2
\end{bmatrix}
\]

\[
t = \frac{c^T \hat{\beta}}{\sqrt{\sigma^2} \sqrt{c^T (X^T X)^{-1} c}}
\]

Large difference: Trustworthy
Small variability: Trustworthy
Many measurements: Trustworthy

And what about this one?

The Model & the Contrast

and the Residual Error

Remember this?
Design Efficiency

Desired P-Value

Design Matrix, X
Contrast, c
Noise level
Temporal autocorrelation

Design Efficiency

Required percent change
Design Efficiency

- Settings for design efficiency calculations
- Correlation matrix
- Eigenvalues
- % change required for each contrast to pass specified z-threshold
- These are the most useful!
When do we have a problem?

- Depends on SNR, and **crucially** the contrasts we are interested in:

  - [1 -1] e.g. vis-tact??
    - no problem
  - [1 1] e.g. average response??
    - no chance
  - [1 0] or [0 1] ?? e.g. visual? or tactile?
    - no chance

<table>
<thead>
<tr>
<th>Effect size required</th>
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<tbody>
<tr>
<td>1.2%</td>
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<td>∞</td>
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</table>
Case Study: Correlated EVs

Scenario:
Investigating whether there is a relationship between a patient’s disease/behavioural scores and their BOLD responses

Problem:
Different scores are likely to be strongly correlated.
Which regions’ responses correlate with disease scores but not age?

Solutions:
Combination of F-tests and t-tests
Correlations, Covariates & Corrections

• Consider a case example:
  ‣ Disease Duration (DD) + age (demeaned)
    ‣ where we want to ‘correct’ for age
Correlations, Covariates & Corrections

• Consider a case example:
  ‣ Disease Duration (DD) + age (demeaned)
    ‣ where we want to ‘correct’ for age
  ‣ If there is correlation between DD and age then it becomes tricky
  ‣ One option is orthogonalisation of DD and age …
Orthogonalisation
Orthogonalisation

DON'T DO IT!
A better alternative to orthogonalisation

- Consider a case example:
  - Disease Duration (DD) + age (demeaned)
    - where we want to ‘correct’ for age
A better alternative to orthogonalisation

Consider a case example:

- Disease Duration (DD) + age (demeaned)
- where we want to ‘correct’ for age

A t-test for a single EV is determined only by variability in BOLD signal that cannot be accounted for by other EVs.

This is a conservative result: only when DD can uniquely explain the measurements will there be a significant result.
A better alternative to orthogonalisation

• Consider a case example:
  ‣ Disease Duration (DD) + age (demeaned)
    ‣ where we want to ‘correct’ for age

\[
\begin{bmatrix}
0 & 1 & 0 \\
0 & 0 & 1 \\
1 & 0 & 0 \\
\end{bmatrix}
\]

t-test

F-test

\[
\begin{bmatrix}
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1 \\
\end{bmatrix}
\]
A better alternative to orthogonalisation

- Consider a case example:
  - Disease Duration (DD) + age (demeaned)
  - where we want to ‘correct’ for age

An F-test finds regions where signal can be explained by *any combination* of EVs.

Will show significant results where either DD or age or both can explain the measurements.
A better alternative to orthogonalisation

**t-test**

\[
\begin{bmatrix}
0 & 1 & 0
\end{bmatrix}
\]

**F-test**

\[
\begin{bmatrix}
1 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0
\end{bmatrix}
\]

Results (a fairly typical example with strong correlation):

*Not significant (t-test)  Significant (F-test)*

**Interpretation:** Significant correlation with both DD and age, but cannot separate the effects as they are too highly correlated and the response to unique portions (if any) are too weak.

**Follow on:** one way to (potentially) separate the effects would be to recruit new subjects such that DD and age were less correlated (need more data to go beyond the above interpretation).
Summary:

• Correlation of EVs makes it difficult for the GLM to assign unique contributions and often leads to no significant results
• Extreme correlation gives rank deficiency
• Problem of correlation depends on the contrast
• Design efficiency gives required % BOLD change to get a significant result per contrast (like power calc.)
• Can also get info about where correlations are
• Orthogonalisation: DON’T DO IT!
• In practice consider F-tests for combined explanatory results as well a t-test (unique contributions)
• Try to break correlations through planning/recruitment
That’s All Folks