Mixed Effects Models: Concepts and Applications in NeuroImaging

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Outline

- *Concepts*
  - The standard fixed effects model
  - What is a mixed effects model, and why do we need it?
  - For simplicity, we will not address the mathematics of parameter estimation, hypothesis testing, or statistical power analysis
    - See the neuroimaging paper referenced in the next slide if you are interested

- *Applications*
  - Mixed effects models in neuroimaging research

References

- *Concepts*
  - A basic tutorial I recommend as an introduction to mixed effects models
    http://www.bodowinter.com/tutorial/bw_LME_tutorial2.pdf

- *Applications*
  - Bernal-Rusiel 2013 – *Statistical analysis of longitudinal neuroimage data with Linear Mixed Effects models*
    https://doi.org/10.1016/j.neuroimage.2012.10.065

Concepts

The standard fixed effects model

- Consider this simple experiment
  - Have a group of participants read a passage out loud, and measure their vocal pitch
  - Construct a model to predict pitch from participant demographics

- Suppose you use a linear model to predict vocal pitch from age and sex
  - $pitch \sim age + sex + \epsilon$
    - Age and sex are the *fixed effects* → these are your familiar independent variables
    - ϵ is the *error term* – it represents random factors that cannot be controlled experimentally
      - Ex: hours of sleep the night before the study, nervousness during experiment, etc…

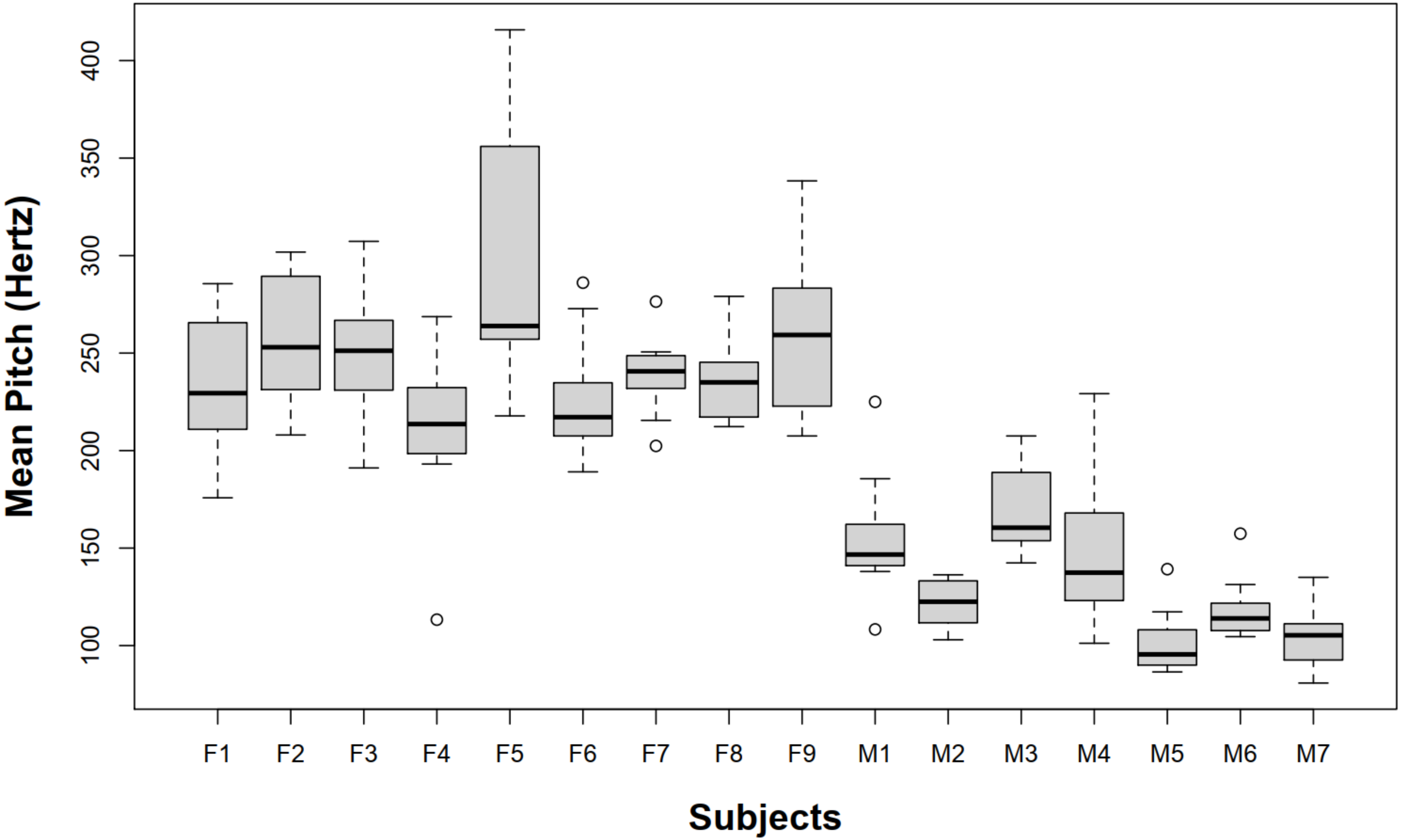
- If each study participant was measured once, then standard statistical models (ex: linear regression) could be used
  - This is because the assumption of independence between observations holds

Motivating the mixed effects model

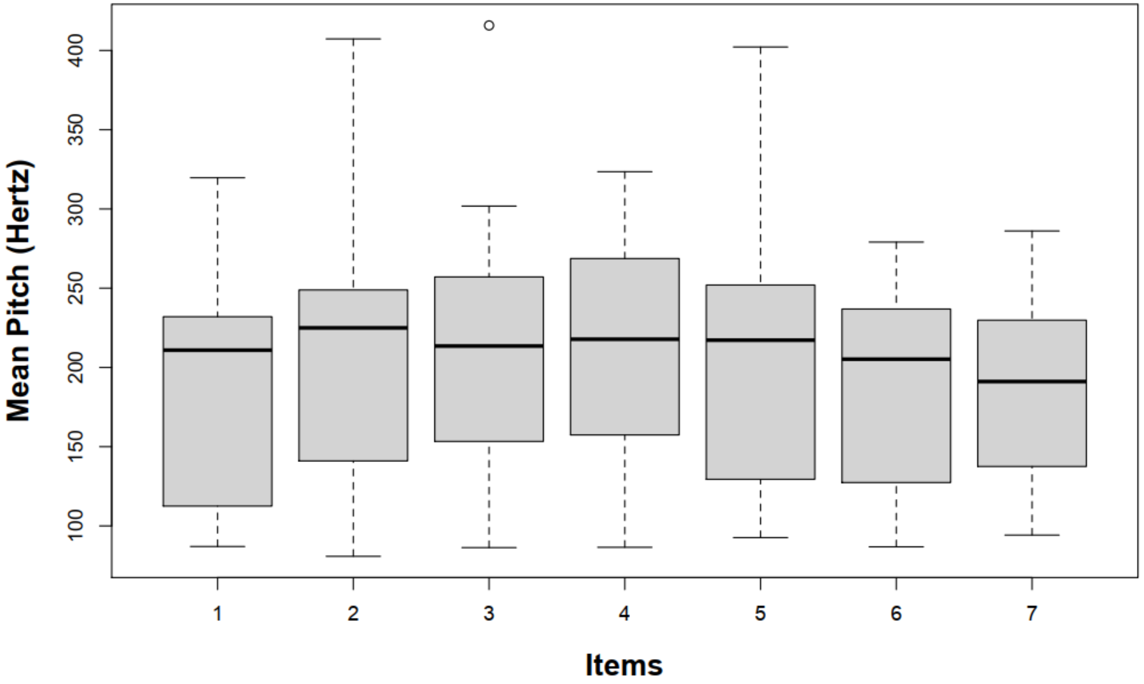
- But what if…
  - *Scenario 1*: each participant's pitch is measured multiple times?
    - Independence between observations no longer holds → measurements are correlated
  - *Scenario 2*: participants were assigned different-themed passages, as the researchers were interested in the effect of theme on pitch?
    - Passages are just a subset of possible passages, therefore modelling them as fixed effects is unnatural

- We can account for these using a *mixed effects* model
  - *Mixed* because we introduce *random effects* into our *fixed effects* model

Motivating the mixed effects model



Motivating the mixed effects model



The mixed effects model

- Each participant has a different baseline pitch, which is known as a *random intercept*
  - Now multiple measurements from a single participant can be accounted for according to their baseline pitch

- Each passage is given a random intercept as well
  - This is done because different passages might elicit different responses, which might affect pitch

- Now suppose the effect of sex on pitch depends on the passage that is being read
  - We can model this elegantly using *random slopes*
  - *Note*: in general if you are unsure of whether to include a random effect in your model, use the likelihood ratio test to compare the likelihood of nested models

The mixed effects model

- The new model is
  - $pitch \sim age + sex + (1|subject) + (1 + sex|passage) + \ \epsilon$
    - Age and sex are included as before
    - $(1|subject)$ contributes the random intercept for each subject
    - $(1 + sex|passage)$ contributes a random intercept for each passage, as well as a random slope to model the effect of sex depending on the passage

Fundamental difference between fixed and random effects

- Fixed effects
  - *Variation in the factor can be captured/exhausted*
    - Ex: sex – only M or F, so we can exhaust the variability in this factor

- Random effects
  - *Measurements obtained are just a subset of the possible measurements we could have obtained*
    - Ex: participants included in the study are just a subset of all the participants that could have been included
    - Ex: passages used are just a subset of the passages that could have been used

Applications in NeuroImaging

Mixed effects models for longitudinal data – key differences

- Time from baseline may be included as an effect in the model
  - This would be the case if time is thought to play an important role in the outcome of interest
    - Ex: Brain atrophy in Alzheimer's patients
  - Here time can be a fixed or random effect, depending on whether rate of atrophy is patient-dependent

- Must also account for variable timing of measurements between patients, as well as subject dropout (causing unbalanced data)

The experiment

- Measure longitudinal hippocampal volume and entorhinal cortex thickness in a dataset consisting of
  - Alzheimer's patients
  - Subjects with mild cognitive impairment
  - Healthy controls

Specification of fixed and random effects

- Fixed effects
  - Time from baseline
  - Clinical group indicator
  - Interaction between time from baseline and clinical group indicator
  - Baseline age
  - Sex
  - APOE genotype status
  - Interaction between APOE genotype status and time from baseline
  - Education (in years)

- Random effects
  - Included based on the likelihood ratio test
  - Random intercept and time slopes were included for all variables

Dataset

Table 1
Longitudinal ADNI sample characteristics.

Variable	Stable HC	Converter HC	Stable MCI	Converter MCI	AD	*p*-value
Number of subjects	210	17	227	166	188	
Baseline age	75.9 ± 5 [60–90]	76.7 ± 5.1 [63–84]	74.8 ± 7.7 [55–90]	74.7 ± 7.1 [55–89]	75.2 ± 7.5 [55–91]	0.3464
Female %	48.1	47.1	33.48	38.6	47.3	<0.01[a]
APOE-ε4 Carriers %	25.7	41.2	43.2	67.5	66	<0.0001[a]
Education	16.1 ± 2.8 [6–20]	16.1 ± 2.8 [12–20]	15.6 ± 3.1 [4–20]	15.7 ± 2.9 [6–20]	14.7 ± 3.2 [4–20]	<0.001

Baseline age (in years) and education values are in mean ± standard deviation; Ranges are listed in square brackets; p-values indicate effects across the groups.
Key: Converter MCI, mild cognitive impairment subjects who convert to Alzheimer's disease; Converter HC, healthy controls who convert to either MCI or Alzheimer's disease.

[a] Using Fisher's exact test; ANOVA-derived p-values were used in the other cases.

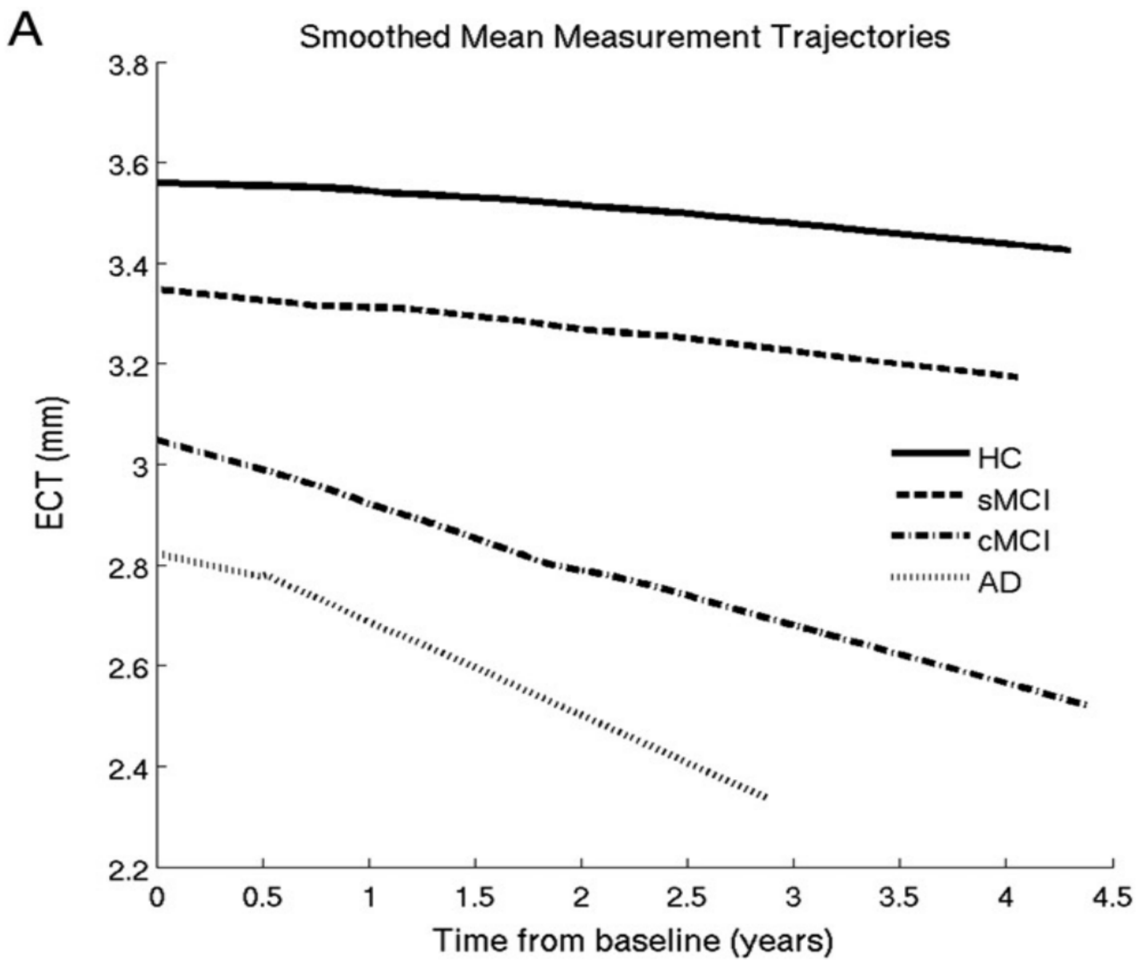
Dataset

Table 2
Number and timing of scans per time point by clinical group (Stable HC, N = 210; Converter HC, N = 17; Stable MCI, N = 227; Converter MCI, N = 166; AD, N = 188).

Time point	Stable HC	Converter HC	Stable MCI	Converter MCI	AD	Time from baseline
Baseline	210	17	227	166	188	0
Year 0.5 (month 6)	197	17	194	161	166	0.58 ± 0.07 [0.21–0.94]
Year 1	183	17	177	153	150	1.08 ± 0.07 [0.68–1.38]
Year 1.5	0	0	153	136	0	1.59 ± 0.08 [1.26–1.92]
Year 2	129	14	108	106	96	2.09 ± 0.10 [1.58–2.88]
Year 3	115	6	68	70	0	3.09 ± 0.09 [2.52–3.45]
Year 4	11	0	3	10	0	4.12 ± 0.09 [3.98–4.38]
Total	845	71	930	802	600	

Time from baseline (in years) is in mean ± standard deviation; ranges are listed in square brackets.

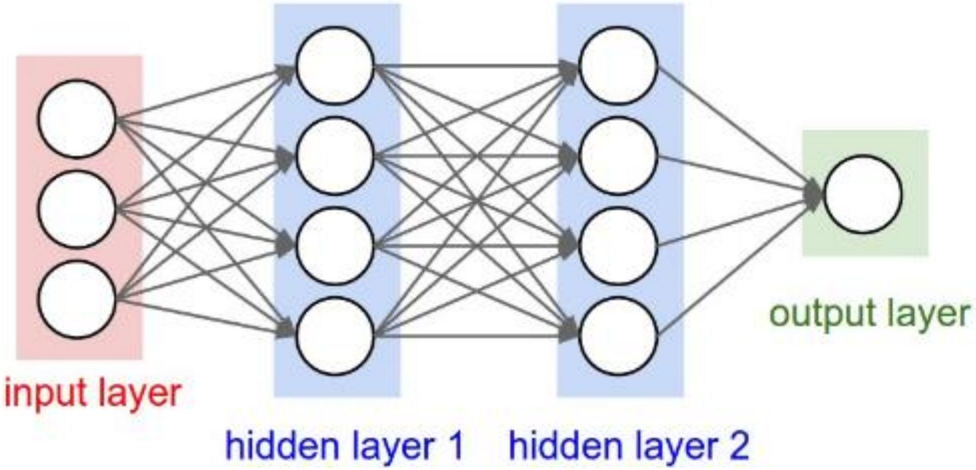
Results


A
Smoothed Mean Measurement Trajectories
3.8
3.6
3.4
3.2
3
2.8
2.6
2.4
2.2
ECT (mm)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Time from baseline (years)
HC
sMCI
cMCI
AD

Looking Ahead

Neural Networks – A Possible Solution?

- Put simply, feedforward neural networks find a function between inputs and outputs
  - Ex: age, sex, clinical features to predict disease

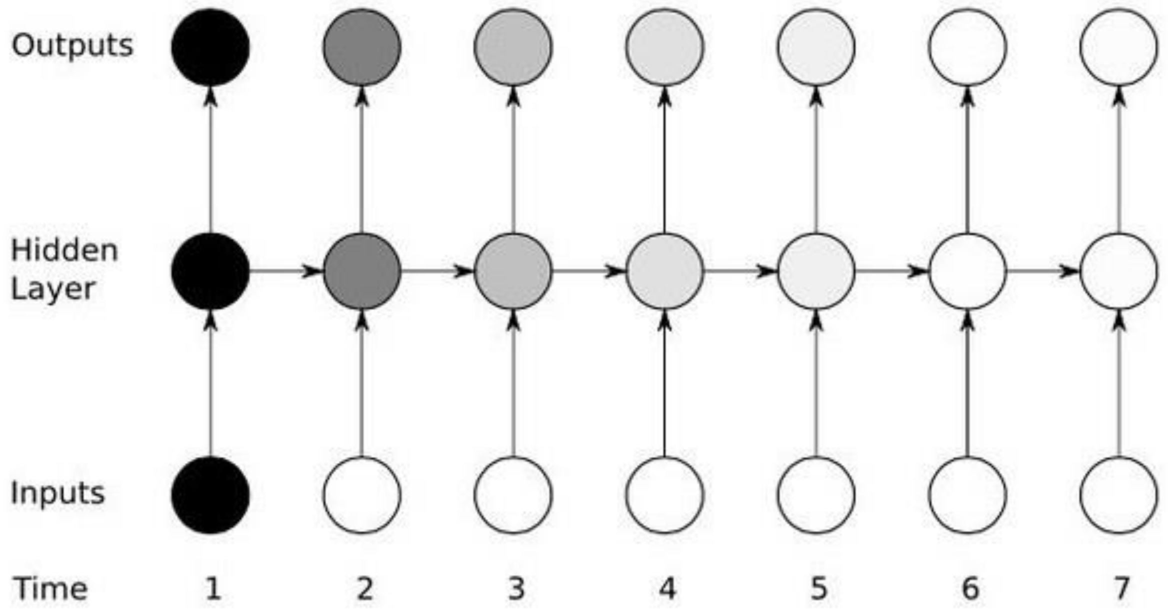


Neural Networks – A Possible Solution?

- For longitudinal data, a similar problem arises for feedforward neural networks as with fixed effects models

- An alternative neural network architecture is the *recurrent neural network* (RNN)
  - This can capture the time-dependencies between measurements

Recurrent Neural Networks



Recurrent Neural Networks