

# Chapter 1

## Motivating Data Sets

# 1.1 Motivating Longitudinal Studies

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- **AIDS:** 467 HIV infected patients who had failed or were intolerant to zidovudine therapy (AZT) (Abrams et al., NEJM, 1994)
- The aim of this study was to compare the efficacy and safety of two alternative antiretroviral drugs, didanosine (ddI) and zalcitabine (ddC)
- Outcomes of interest:
  - ▷ CD4 cell count measurements at baseline, 2, 6, 12 and 18 months
  - ▷ randomized treatment: 230 patients ddI and 237 ddC
  - ▷ prevOI: previous opportunistic infections

# 1.1 Motivating Longitudinal Studies (cont'd)



# 1.1 Motivating Longitudinal Studies (cont'd)

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- Research Questions:
  - ▷ How CD4 cell count evolves in time for this cohort of patients?
  - ▷ Does treatment improve average longitudinal evolutions?

## 1.1 Motivating Longitudinal Studies (cont'd)

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- **PBC:** Primary Biliary Cirrhosis:
  - ▷ a chronic, fatal but rare liver disease
  - ▷ characterized by inflammatory destruction of the small bile ducts within the liver
- Data collected by Mayo Clinic from 1974 to 1984 (Murtaugh et al., Hepatology, 1994)
- Outcomes of interest:
  - ▷ longitudinal serum bilirubin, serum cholesterol, prothrombin time
  - ▷ randomized treatment: 158 patients received D-penicillamine and 154 placebo

# 1.1 Motivating Longitudinal Studies (cont'd)



## 1.1 Motivating Longitudinal Studies (cont'd)

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- Research Questions:
  - ▷ Do men have higher serum bilirubin during follow-up than women?
  - ▷ Is there a difference in the average longitudinal evolutions of serum bilirubin between the two treatments when we correct for age and gender at baseline?

## 1.1 Motivating Longitudinal Studies (cont'd)

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- **Prothro:** Prednisone versus placebo in liver cirrhosis patients
  - ▷ slowly progressing disease in which healthy liver tissue is replaced with scar tissue, eventually preventing the liver from functioning properly
- Randomized trial in Denmark (Andersen et al., Springer, 1993)
- Outcomes of interest:
  - ▷ randomized treatment: 237 patients received prednisone and 251 placebo
  - ▷ longitudinal prothrombin times



# 1.1 Motivating Longitudinal Studies (cont'd)



## 1.1 Motivating Longitudinal Studies (cont'd)

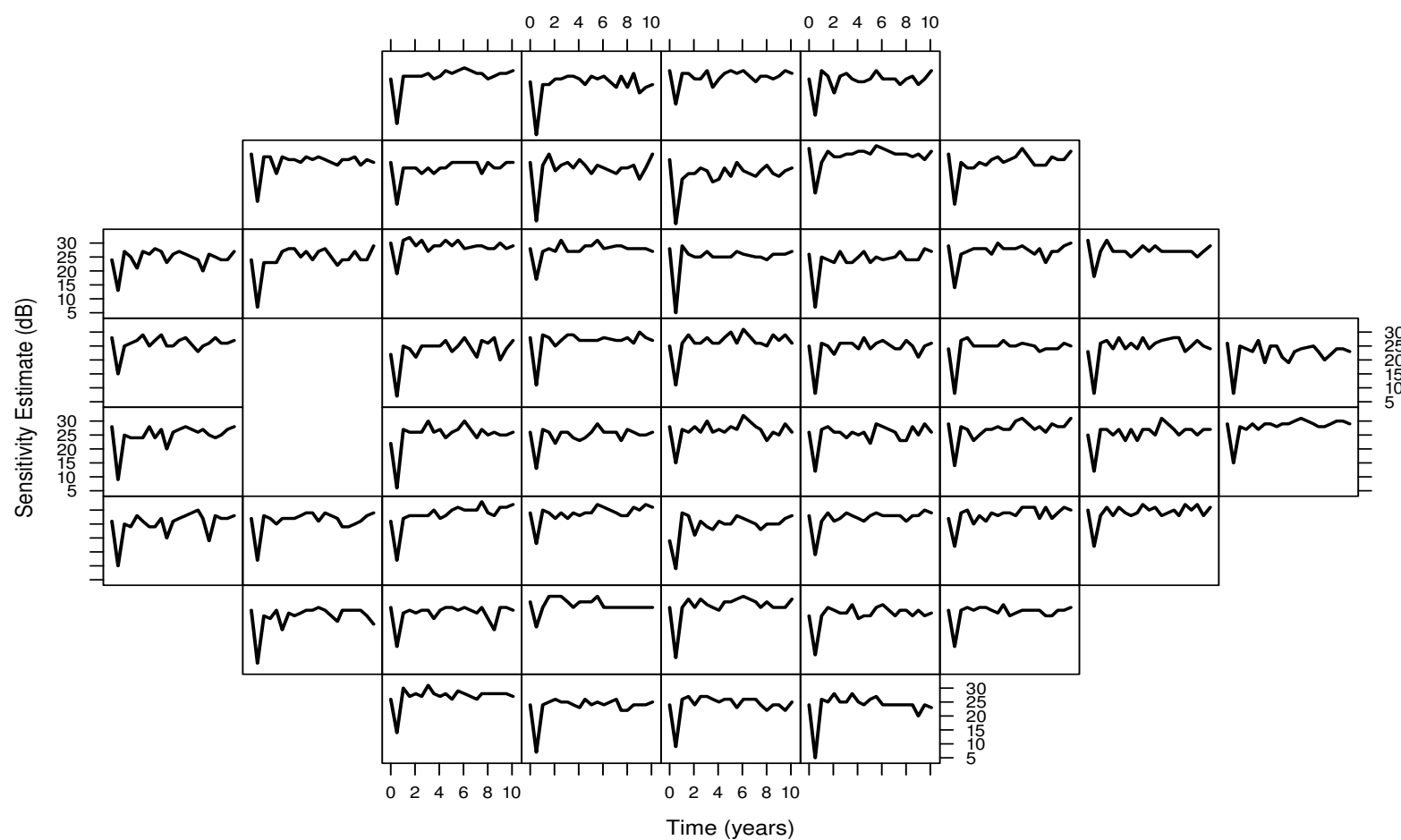
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- **Glaucoma:** A group of eye conditions resulting in optic nerve damage, which may cause loss of vision
- Ongoing prospective cohort study on 139 patients (80% men) conducted by the Rotterdam Eye Hospital in the Netherlands <http://rod-rep.com>
- Outcome of interest:
  - ▷ Visual field (VF) sensitivity collected at approximately 6-months intervals

# 1.1 Motivating Longitudinal Studies (cont'd)



# 1.1 Motivating Longitudinal Studies (cont'd)



## 1.1 Motivating Longitudinal Studies (cont'd)

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- Research Questions:
  - ▷ Study disease progression using VF sensitivity
  - ▷ Predict rate of progression for future patients

## 1.2 Features of Longitudinal Data

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- Repeated evaluations of the same outcome in each subject in time
  - ▷ CD4 cell count in HIV-infected patients
  - ▷ serum bilirubin in PBC patients
- Visiting process
  - ▷ some times fixed by design (e.g., in randomized trials) but often not everybody adheres to them
  - ▷ completely determined by the physicians and/or the patients

## 1.2 Features of Longitudinal Data (cont'd)

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**Measurements on the same subject are expected to be (positively) correlated**

- This implies that standard statistical tools, such as the  $t$ -test and simple linear regression that assume independent observations, are not optimal for longitudinal data analysis

## 1.2 Features of Longitudinal Data (cont'd)

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- Let's see why: The simplest case of longitudinal data are paired data
- Example: We consider the baseline and 6-month longitudinal measurements of square root CD4 cell count from the AIDS dataset

	n	mean	sd
<i>month</i> = 0	294	7.73	4.69
<i>month</i> = 6	294	6.71	4.96



## 1.2 Features of Longitudinal Data (cont'd)

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- There is an average decrease of about 1 unit
- The classical analysis of paired data is based on comparisons within subjects:

$$\Delta_i = Y_i(t = 0) - Y_i(t = 6), \quad i = 1, \dots, n$$

- A positive  $\Delta_i$  corresponds to a decrease of the square root CD4 cell count, while a negative  $\Delta_i$  is equivalent to an increase
- Testing for a time effect is now equivalent to testing whether the average difference  $\mu_{\Delta}$  equals zero

## 1.2 Features of Longitudinal Data (cont'd)

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- The paired  $t$ -test yields

Paired  $t$ -test

```
data: CD4 by obstime t = 6.472, df = 293, p-value = 4.057e-10
alternative hypothesis: true difference in means is not equal to 0 95 percent
confidence interval:
 0.7105585 1.3315439
sample estimates: mean of the differences
                1.021051
```

## 1.2 Features of Longitudinal Data (cont'd)

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- What if we had ignored the paired nature of the data?
- We then could have used a two-sample (unpaired)  $t$ -test to compare the average CD cell count at the two time points

Welch Two Sample t-test

```
data: CD4 by obstime t = 2.565, df = 584.229, p-value = 0.01056
alternative hypothesis: true difference in means is not equal to 0 95 percent
confidence interval:
 0.2392406 1.8028617
sample estimates: mean in group 0 mean in group 6
      7.730128      6.709077
```

## 1.2 Features of Longitudinal Data (cont'd)

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- We would still have found a significant difference ( $p = 0.0106$ ), but the p-value would have been many times larger compared to the one obtained using the paired  $t$ -test
- The two-sample  $t$ -test does not take into account that the measurements are not independent
  - ▷  $p$ -values **wrongly** too small for *between subjects* effects
  - ▷  $p$ -values **wrongly** too large for *within subjects* effects
- The different effects
  - ▷ *between subjects*: examine differences between subjects (e.g., males vs females)
  - ▷ *within subjects*: examine how much subjects tend to change over time

## 1.2 Features of Longitudinal Data (cont'd)

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- This illustrates that classical statistical models which assume independent observations will not be optimal for the analysis of clustered data

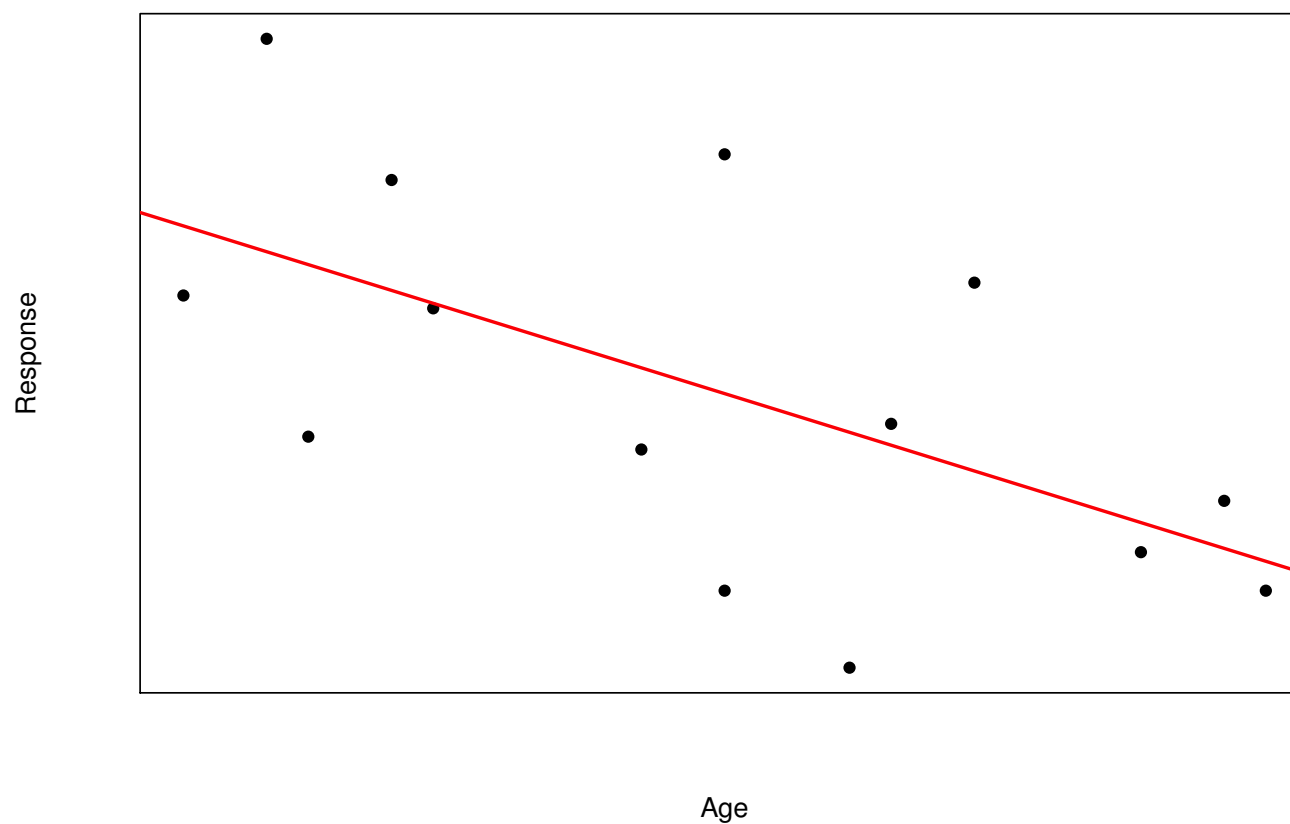
## 1.2 Features of Longitudinal Data (cont'd)

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- Longitudinal studies allow to investigate
  1. how treatment means differ at specific time points, e.g., at the end of the study (*cross-sectional effect*)
  2. how treatment means or differences between means of treatments change over time (*longitudinal effect*)
- An example: Suppose it is of interest to study the relation between some response  $Y$  and age
  - ▷ a cross-sectional study yields the following data:

## 1.2 Features of Longitudinal Data (cont'd)

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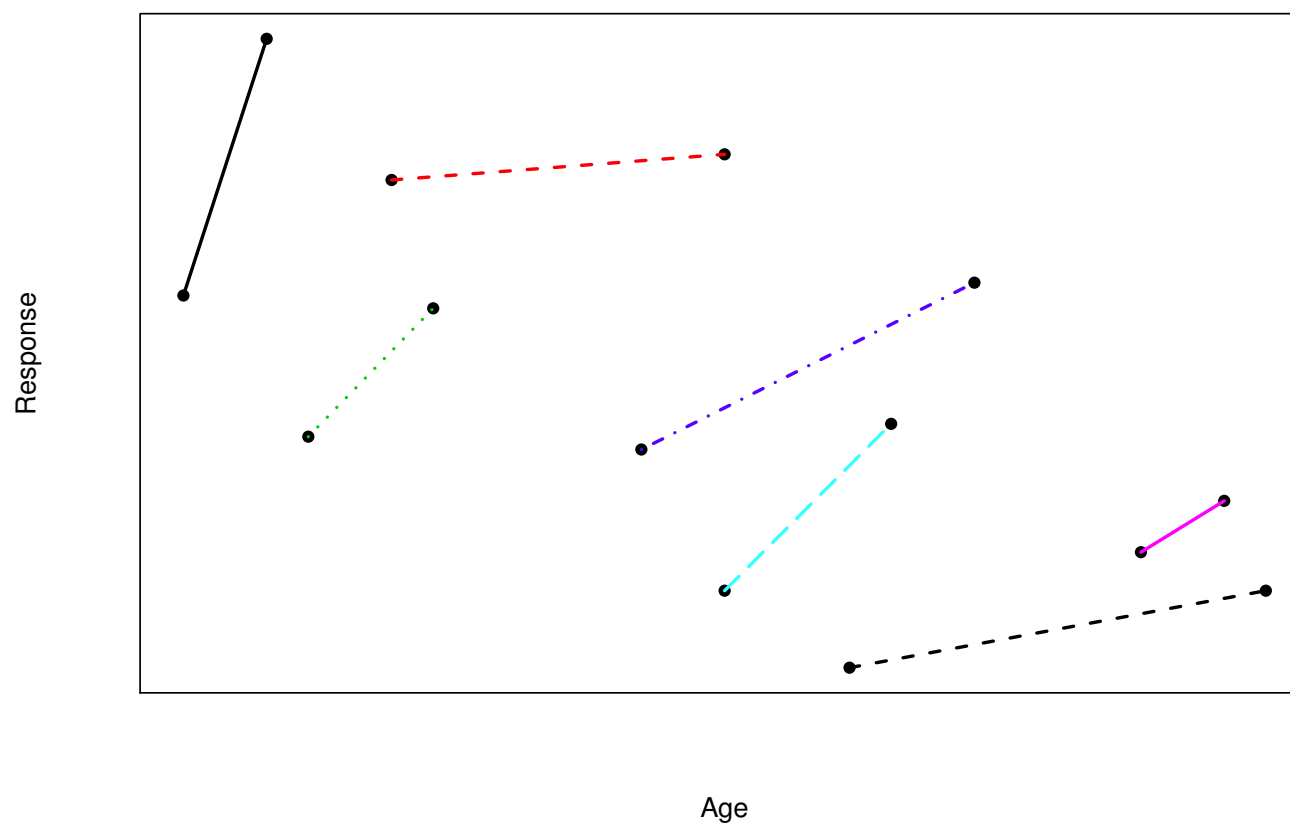
## 1.2 Features of Longitudinal Data (cont'd)

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- The graph clearly suggests a negative relation between  $Y$  and age
- **Nevertheless**, exactly the same observations also could have been obtained in a longitudinal study, with 2 measurements per subject



## 1.2 Features of Longitudinal Data (cont'd)



## 1.2 Features of Longitudinal Data (cont'd)

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**Are we now still inclined to conclude that there is a negative relation between  $Y$  and age?**

- Conclusion: Longitudinal data allow to distinguish differences between subjects from changes within subjects

## 1.3 Review of Key Points

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- Grouped & longitudinal data: Features
  - ▷ measurements on the same subject are correlated
  - ▷ allow to distinguish within and between subjects effects