

Chapter 1

Motivating Data Sets

1.1 Motivating Longitudinal Studies

- **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)

- 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)

- **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)

- 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 when we correct for age differences at baseline and gender differences during follow-up?

1.1 Motivating Longitudinal Studies (cont'd)

- **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: 158 patients received D-penicillamine and 154 placebo
 - ▷ longitudinal prothrombin times

1.1 Motivating Longitudinal Studies (cont'd)



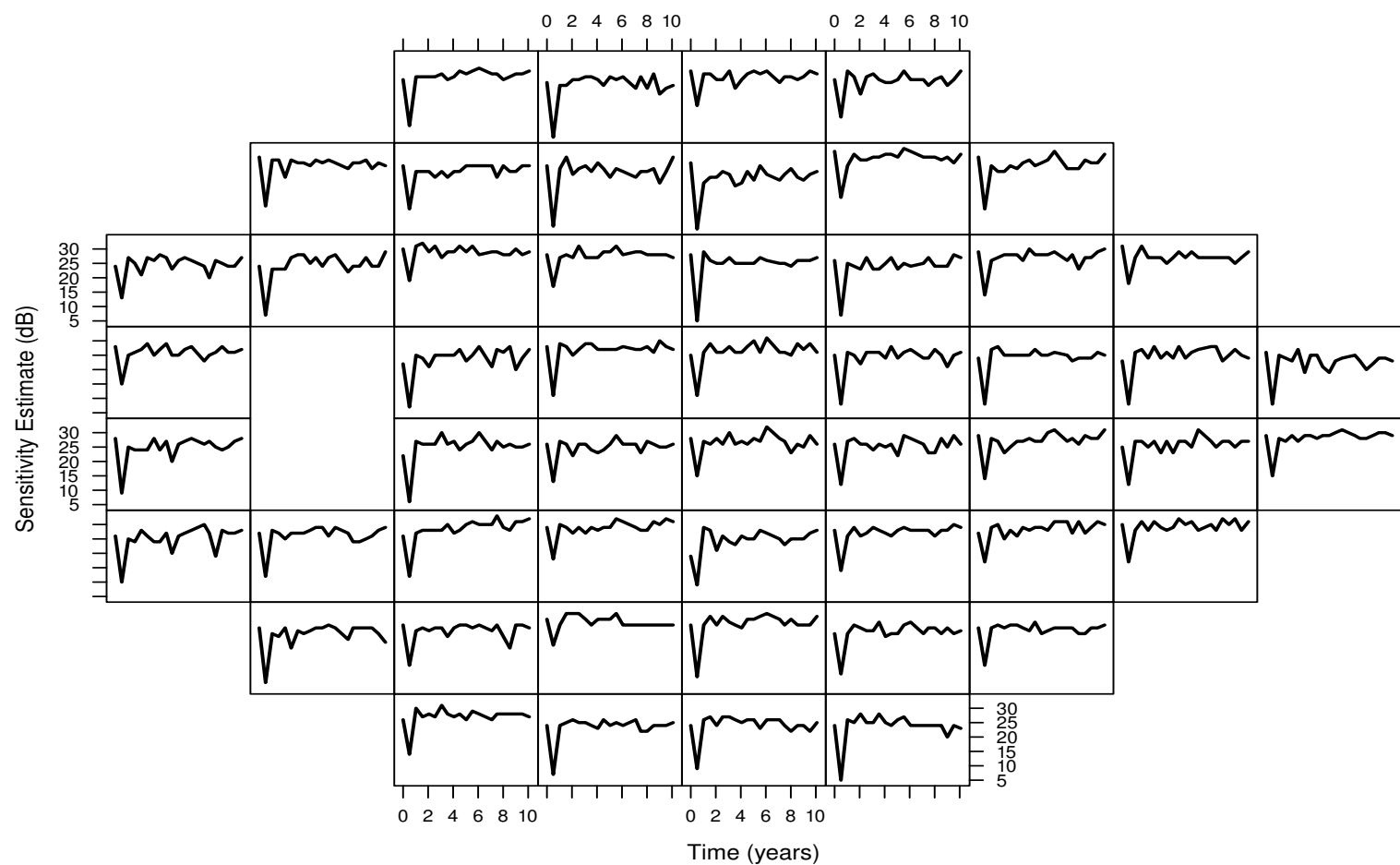
1.1 Motivating Longitudinal Studies (cont'd)

- **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)

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

1.2 Features of Longitudinal Data

- 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)

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)

- 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)

- 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 Δ_i corresponds to a decrease of the square root CD4 cell count, while a negative Δ_i is equivalent to an increase
- Testing for a time effect is now equivalent to testing whether the average difference μ_{Δ} equals zero

1.2 Features of Longitudinal Data (cont'd)

- 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)

- 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)

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

1.2 Features of Longitudinal Data (cont'd)

- 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)



1.2 Features of Longitudinal Data (cont'd)

- 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)

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

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