

AS TIME GOES BY...

An Introduction to Methods for the Analysis of Longitudinal Data

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Slide 1

OUTLINE

1. **Some examples**
2. **Some *ad hoc* approaches (and why they might not be so good...)**
3. **How do longitudinal data happen? – A conceptualization**
4. **A formal statistical approach**
5. **Back to the examples**
6. **Conclusions**

Slide 2

1. Some examples

Longitudinal studies in health sciences research: Studies where each participant is observed *over time* are *commonplace*

- *Clinical trials*
- *Observational studies*
- *Different objectives*, depending on the setting...
- *Different complications*, depending on the setting...

In general: Data are collected over time because interest focuses on what happens over time!

Slide 3

First, an “ideal” situation...

“World-famous” dental study: Pothoff and Roy (1964)

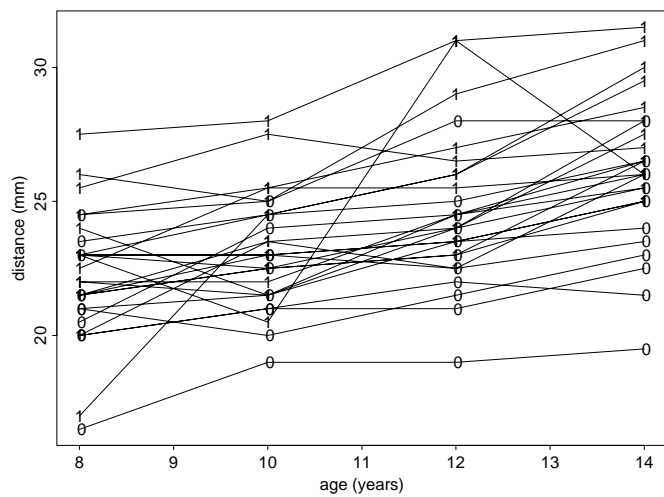
- 27 children, 16 boys, 11 girls
- On each child, *distance* (mm) from the center of the pituitary to the pteryomaxillary fissure measured *on each child* at ages 8, 10, 12, and 14 years of age
- A measure of *growth*

Questions of interest:

- Do things *change* over time?
- Understand *pattern of change* (*growth*)
- Is the pattern *different* for boys and girls? *How?*

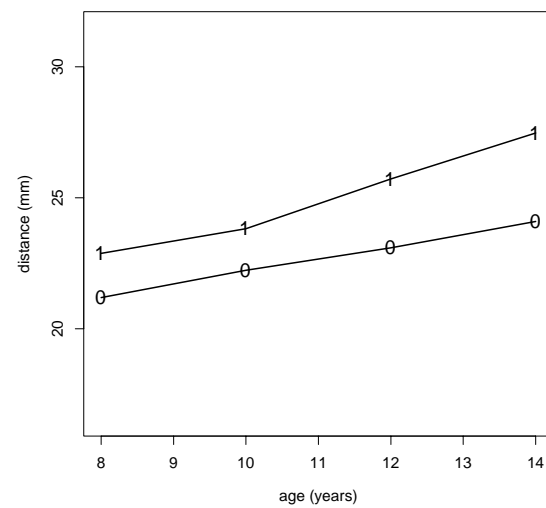
Slide 4

All data: 0 = girl, 1 = boy



Slide 5

Sample average dental distances: 0 = all girls, 1 = all boys



Slide 6

Remarks:

- *All children have all 4 measurements* (no *missing* data, “*balanced*”)
- Overall pattern of *increasing distance measurements* for boys and girls
- *More specifically*, the pattern for *most children* follows a *rough straight line* increase (with some “*jitter*”)
- And *average distance* (across boys and across girls) follows an approximate *straight line* pattern (although that for boys looks like it might *curve*...)

Now for some not-so-ideal examples...

Slide 7

The COMPARE study: Study the *anti-aggregatory effects* (*pharmacodynamics*) of current platelet glycoprotein IIb/IIIa receptor antagonists during/after percutaneous coronary intervention (PCI) in patients with acute coronary syndromes (ACS) (Batchelor et al., *Circulation*, 2002)

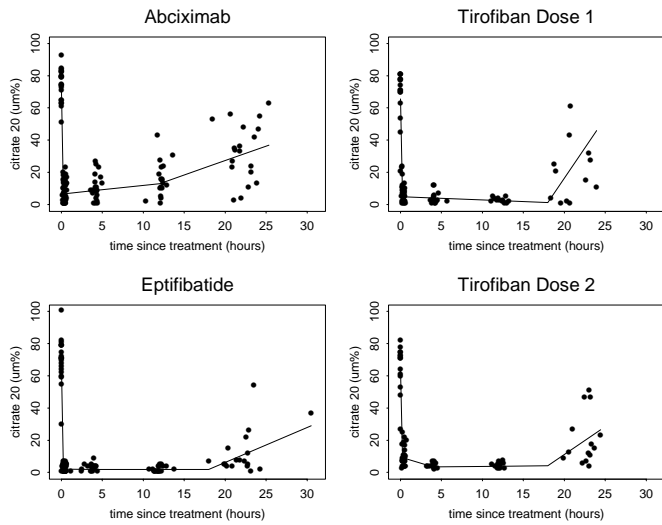
- 70 PCI patients *randomized* to abciximab, eptifibatide, tirofiban (2 doses) at Duke University Medical Center
- *Platelet aggregation* in response to adenosine diphosphate measured following treatment initiation (bolus + 12- or 18-hour post-PCI infusion)

More specifically, questions of interest:

- Do *patterns of % aggregation differ* across regimens? *How?*

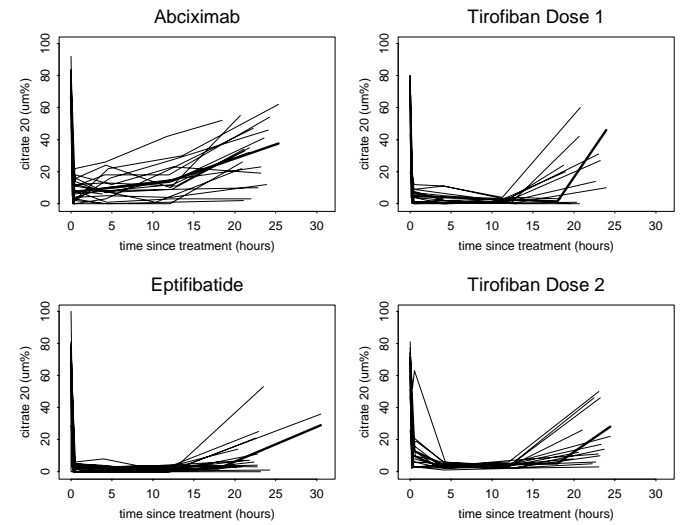
Slide 8

% Aggregation data:



Slide 9

% Aggregation profiles: "Connect the dots" for each subject



Slide 10

Remarks:

- All regimens show *early rapid decline* to 30 minutes, “*rebound*” at end of infusion
- *Eptifibatide, tirofiban* show “*flat*” pattern from about 1 hour to end of infusion
- But *abciximab* shows *increasing* pattern (less inhibition) with *more variation*
- *Despite protocol*, % aggregation *NOT* measured at the same times for each subject (not “*balanced*”)
- So *can't* take averages (*different time points*)

Slide 11

AIDS Clinical Trials Group (ACTG) 175: *Clinical trial* in asymptomatic HIV-infected patients

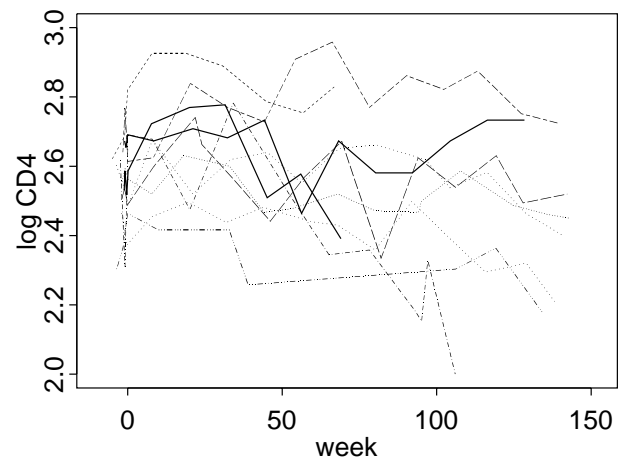
- 2467 subjects, 1991–1994
- Randomized to *four treatment regimens* (ZDV,ddl, ZDV+ddl,ZDV+ddC)
- *Primary endpoint:* Time to AIDS or death
- *In addition:* CD4 counts approximately *every 12 weeks*

Questions of interest: *Subsequent* to primary analysis

- *Pattern of change* of CD4
- *Different* across treatment regimens? *How?*

Slide 12

log CD4 profiles: 10 randomly chosen ZDV subjects



Slide 13

Remarks:

- Individual CD4 profiles “jump around” (“noisy”) but many show a decrease over time
- Different subjects have CD4 measurements at different times (not “balanced”)
- Some subjects drop out of the study, are administratively censored, or, worse, die \Rightarrow no CD4 available
- Can't take averages (different time points); regardless, this is “not fair” because averages at later times reflect dropout/death (only the strong survive!)

Slide 14

ACTG 175: *In fact*, a more *complicated question*

- Are *features* of pattern of CD4 *associated with prognosis*?
- E.g., is the extent of *decrease* in CD4 trajectory over time associated with *time to AIDS/death*?
- Is CD4 a good “*surrogate marker*?”

Slide 15

Pharmacokinetics of theophylline:

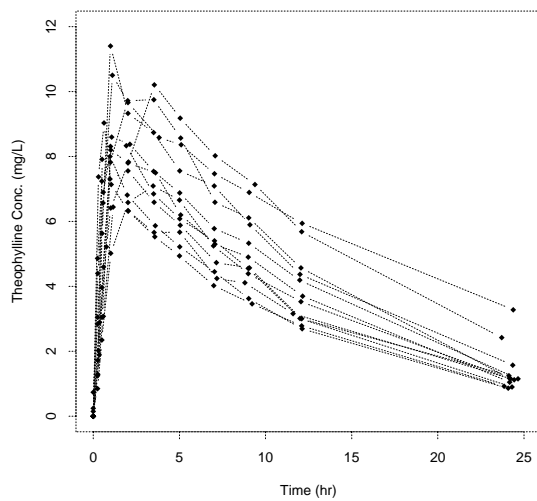
- 12 subjects each given *oral dose* at time 0
- *Blood samples* at 10 time points over next 25 hours, *assayed* for *theophylline concentration*

Questions of interest:

- Understand processes of *absorption, elimination, distribution* in the *population* of subjects like these (e.g., dosing recommendations)

Slide 16

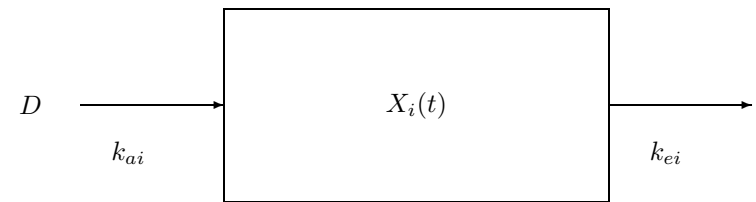
Data for 12 subjects: Concentration vs. time



Slide 17

Standard practice: A “*theoretical model*” for concentration-time for any subject

- Represent the body of *i*th subject by a *one compartment model with first-order absorption and elimination* following oral dose *D*



Concentration at time *t*:

$$C_i(t) = \frac{k_{ai}D}{V_i(k_{ai} - k_{ei})} \{e^{-k_{ei}t} - e^{-k_{ai}t}\}$$

Slide 18

Remarks:

- Fractional absorption rate k_{ai} , fractional elimination rate k_{ei} , volume of distribution V_i characterize *absorption, elimination, distribution* processes for subject i
- Concentration-time patterns *same shape*, but *differ* for different subjects
- \Rightarrow values of k_{ai} , k_{ei} , V_i *vary* in the population of subjects
- \Rightarrow Learn about *average values* and *extent of variation* of k_{ai} , k_{ei} , V_i
- A *different* kind of question, and one that needs to refer to the *pharmacokinetic one-compartment model*...

Slide 19

Questions, issues, complications...

- *Characterize* and *compare patterns of change*
- Investigate *associations* that *evolve over time*
- Learn about features *underlying* observed patterns
- *Different subjects* observed at *different time points*
- *Missing information, dropout, censoring*

What to do???

Slide 20

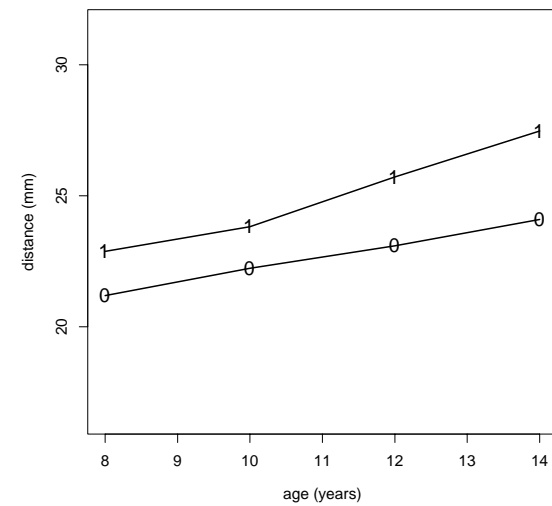
2. Some *ad hoc* approaches

Dental study: *Recall*

- 27 children, 16 boys, 11 girls
- *Distance* measured at 8, 10, 12, 14 years of age on *all children*
- *No missing observations*

Slide 21

Sample average dental distances: 0 = all girls, 1 = all boys



Slide 22

Do things change over time?

Ad hoc approach: For each gender

- Compare *mean* at age 8 to *mean at subsequent ages*
- Age 10 vs. 8, age 12 vs. 8, age 14 vs. 8 (*paired t-tests*)
- *P-values for boys*: 0.15, 0.0003, 0.0001
- *Conclusion? Multiple comparisons?*
- *How to characterize “change?”*

Slide 23

Are the patterns different for boys and girls?

Ad hoc approach: Cross-sectional analysis at each age

- Compare *means* boys vs. girls at *each age* 8, 10, 12, 14 (*two-sample t-tests*)
- *P-values*: 0.08, 0.06, 0.01, 0.001
- *Conclusion? Multiple comparisons?*
- How to “*put this together*” to say something about the *differences in patterns* and *how* they differ? *What are the patterns, anyway?*

Observation: *Individual child* and *gender-averaged* trajectories look like *straight lines*...

- ⇒ Suggests a particular kind of *pattern*
- Can this be *exploited?*

Slide 24

Ad hoc approaches:

- Estimate an *intercept* and *slope* by *least squares* from the boy data and girl data
- Is there a *change over time*? Are boy and girl slopes *different from 0*? (p-values 0.002, 0.001)
- Are the *patterns of change different*? *Compare the slopes* (p-value 0.13)
- Or, *another way* – estimate an *intercept* and *slope* for *each child* using *least squares*, compare *average slopes* to zero and to each other...

Can do this more formally and correctly...

Slide 25

COMPARE study: Recall

- Patterns much more *complicated*
- *Different subjects* measured at *different times*!

ACTG 175: *Same issues*, and, *worse*,

- Subjects *drop out, die*

Clearly, these *ad hoc* fixes won't do here. . .

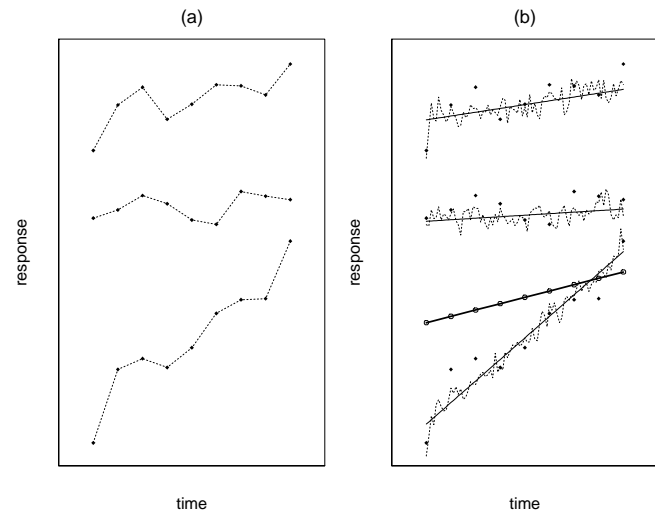
Slide 26

3. How do longitudinal data happen?

A better way: *Conceptualize* how longitudinal data come about

- ... and use as a basis for a *formal approach*

Slide 27



Slide 28

Features:

- Each subject has an “*inherent trend*” or “*trajectory*”
- Actual values might “*fluctuate*” about the trend
- *Errors in measurement* in ascertaining values might occur

Remarks:

- Measurements on the *same subject* tend to be “*high*” or “*low*” together ⇒ measurements on the *same subject* are “*more alike*” than measurements from *different subjects*
- Values *close together in time* might tend to “*fluctuate*” *similarly* ⇒ Measurements on a given subject are “*more alike*” the *closer together* they are in time
- So *values* on the *same subject* show *association*; i.e. *correlation*
- ... and suggests that we should think of data *in groups*, according to *subject*

Slide 29

4. A formal statistical approach

The idea: Use these observations to propose a *model* for how longitudinal data come about

- ... and use the model as the basis for *statistical methods*
- The model describes *patterns of change* as *trends*; e.g., a *straight line*
- The model acknowledges *associations* among observations on the *same subject*
- *More formally*, the model allows observations from the same subject to be *correlated*

Slide 30

Illustration: The dental study

- *Distance measurements* for subject i : y_{ij} at ages $t_{ij} = 8, 10, 12, 14$
- Distance values don't really *fluctuate*, but probably increase pretty smoothly
- *Errors* in measuring distance are likely committed each time
- Each child has its own *growth trajectory* in the form of a *straight line* with *intercept* β_{0i} and *slope* β_{1i}

$$y_{ij} = \beta_{0i} + \beta_{1i}t_{ij} + e_{ij}$$

- e_{ij} represents the “*error*” in measurement

Slide 31

$$y_{ij} = \beta_{0i} + \beta_{1i}t_{ij} + e_{ij}$$

- There is an *average intercept* and *slope* across boys, and similarly across girls – i 's *deviate from these*

$$\beta_{0i} = \beta_{B0} + b_{0i}, \quad \beta_{1i} = \beta_{B1} + b_{1i}$$

$$\beta_{0i} = \beta_{G0} + b_{0i}, \quad \beta_{1i} = \beta_{G1} + b_{1i}$$

- So if β_{0i} is “*high*” relative to β_{0B} , (b_{0i} is *positive*), then i 's trajectory will be “*high*” relative to other boys
- β_{1i} may be *steeper* or *shallower* than the average increase
- ... and all of i 's measurements depend β_{0i} and β_{1i} , so they are *associated* (*correlated*)
- Like an ordinary *regression model*, only *fancier*... “*Linear mixed effects model*”
- *Can fit* the model to data, carry out *tests*, etc. with *widely-used software*

Slide 32

$$y_{ij} = \beta_{0i} + \beta_{1i}t_{ij} + e_{ij}$$

$$\beta_{0i} = \beta_{B0} + b_{0i}, \quad \beta_{1i} = \beta_{B1} + b_{1i}$$

$$\beta_{0i} = \beta_{G0} + b_{0i}, \quad \beta_{1i} = \beta_{G1} + b_{1i}$$

Result: *Questions of interest*

- Is there a *change* in distance over time for boys and girls? $\Rightarrow \beta_{B1} = 0? \beta_{G1} = 0?$ (p-values **0.0001**, **0.0001**)
- Is the *pattern of change* the same? $\Rightarrow \beta_{B1} = \beta_{G1}?$ (p-value **0.01**)
- *In fact:* We can *estimate* these slopes \Rightarrow *quantify* the patterns of change; *more information!*
- Other questions: Is there evidence that the average trend for boys *curves*? Is the average trend for boys *higher* than for girls?

Slide 33

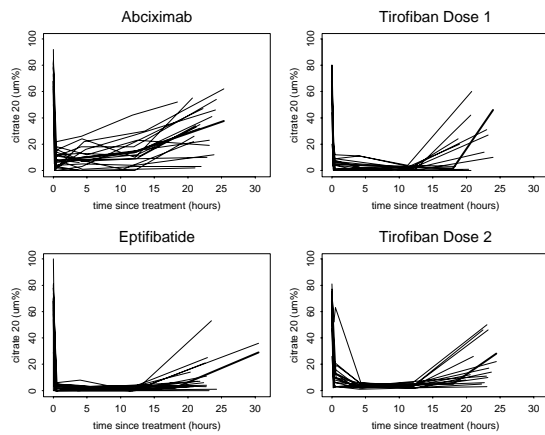
Remarks:

- Because we *model smooth trends*, same timing for all subjects *doesn't matter*
- *Naturally* accounts for the *associations* we expect
- *Requires assumption of trend*, but trends *are often seen*
- "*Makes the most*" of the data we have

Slide 34

5. Back to the examples

COMPARE % Aggregation profiles:



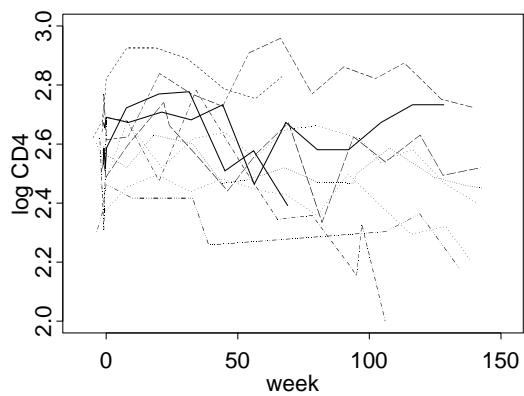
Slide 35

Model: “*piecewise*” straight lines for each phase

- Take into account *differences in variation*
- *Automatically* takes into account differences in timing
- *Compare slopes* in the inhibitory phase

Slide 36

ACTG 175 log CD4 profiles:



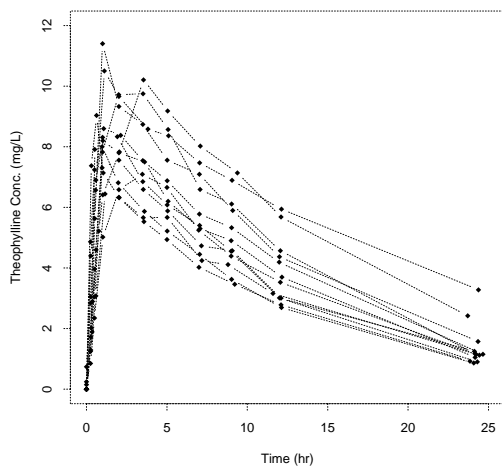
Slide 37

Model: Straight lines or curves

- *Complication* – *censoring, death* curtails profiles
- *Extend the model* – *Cox proportional hazards model*, where hazard for i at time t *depends on* trend $\beta_{0i} + \beta_{1i}t$
- Allows taking account of *censoring, death*
- ... *AND* allows assessment of *relationship* to CD4 trajectory

Slide 38

Theophylline PK profiles:



Slide 39

Individual trend: $C_i(t) = \frac{k_{ai}D}{V_i(k_{ai} - k_{ei})} \{e^{-k_{ei}t} - e^{-k_{ai}t}\}$

Individual PK parameters: Vary about average values

$$k_{ai} = k_a + b_{k_a,i}, \quad k_{ei} = k_e + b_{k_e,i}, \quad V_i = V + b_{V,i}$$

- Learn about average values \Rightarrow Estimate k_a, k_e, V
- Can also estimate variation of these

Slide 40

6. Conclusions

- Information in longitudinal data is often not *fully exploited* because *ad hoc* methods are used
- *By conceptualizing* longitudinal data, we gain a framework to “*make the most*”
- This has been only a *conceptual introduction* to an approach that tries to do so
- Focused here on *continuous measurements*, but similar methods exist for yes/no, categorical outcomes

Talk to your friendly neighborhood statistician!!!

Slide 41