Repeated Measures Design

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Common design: Repeated measures designs

- Take measurements on same subject over time or under different conditions.
- Same basic idea as a randomized block design:
  - treatment effects measured on ``units'' that are similar as possible.

Repeated measures designs Advantages

- Precision determined by variation within same subject;
- May be the only design that answers the questions of interest.
  - For example, how do measurements on an individual change over time?

Repeated measures designs Disadvantages

- May not be feasible
- May not give realistic assessments of treatment effects
- Analyses more difficult
  - usually need to take into account associations between observations taken from same individual

Repeated measures designs
Cross-over Designs

- Subjects receive every treatment
- Most common is ``two-period, two-treatment''
  - Subjects are randomly assigned to receive either
    - A in period 1, B in period 2 or
    - B in period 1, A in period 2

Repeated measures designs
Cross-over Designs

- Important assumption: No carry-over effects
  - effect of treatment received in each period is not affected by treatment received in previous periods.
- To minimize possibility of carry-over effects
  - ‘`wash-out'' time between the periods in which treatments are received.

Cross-over designs: Example

- Treatments: Impermeable (IP) / Semi-Permeable (SP)
- Outcomes: Skin temperature, heat storage, oxygen consumption
- Protocol:
  - 6 men studied under both types of clothing.
  - 3 men randomized to order (IP, SP), 3 men to (SP, IP)

Rissanen and Rintamaki (1997) Ergonomics p. 141-150.

Cross-over designs: Example

- Why a crossover design and not a completely randomized design ?
- Would expect large amounts of variability in heat storage, oxygen consumption, etc. from different men.
- Would expect small variability in these measures from the same man at two different times

Cross-over designs: Example 2

- Effects of fluids on exercise capacity.
- Treatments: (N) no drink, (W) water, (I) isotonic glucose electrolyte and (H) hypotonic glucose electrolyte.
- Outcome is ``time to exhaustion.''
- 12 subjects available.

Cross-over designs: Example 2 Possible designs

- Completely randomized?
- Randomized block?
- Cross-over:
  - Each subject observed under each condition
  - Randomize order.
  - One week period between observations.

Cross-over designs: Example 2

- Precision determined by variation in ``time to exhaustion'' by a subject over multiple occasions.
  - Avoids basing precision on variation in time to exhaustion between different subjects

Cross-over designs: Examples

- Both examples illustrate importance of
  - ``wash-out period'' and
  - randomizing/balancing the order that treatments are applied.

Completely randomized design or randomized block design or a cross-over design?

- Is the natural variability within a subject likely to be small relative to the natural variability across subjects?
- Are there likely to be carry-over effects?
- Are there likely to be ``drop-outs''?
- Is a cross-over design feasible?

Completely randomized design or randomized block design or a cross-over design?

- No definitive statistical answer to the question.
- Answer depends on knowledge of
  - experimental material and
  - the treatments to be studied

Measurements over time (longitudinal studies)

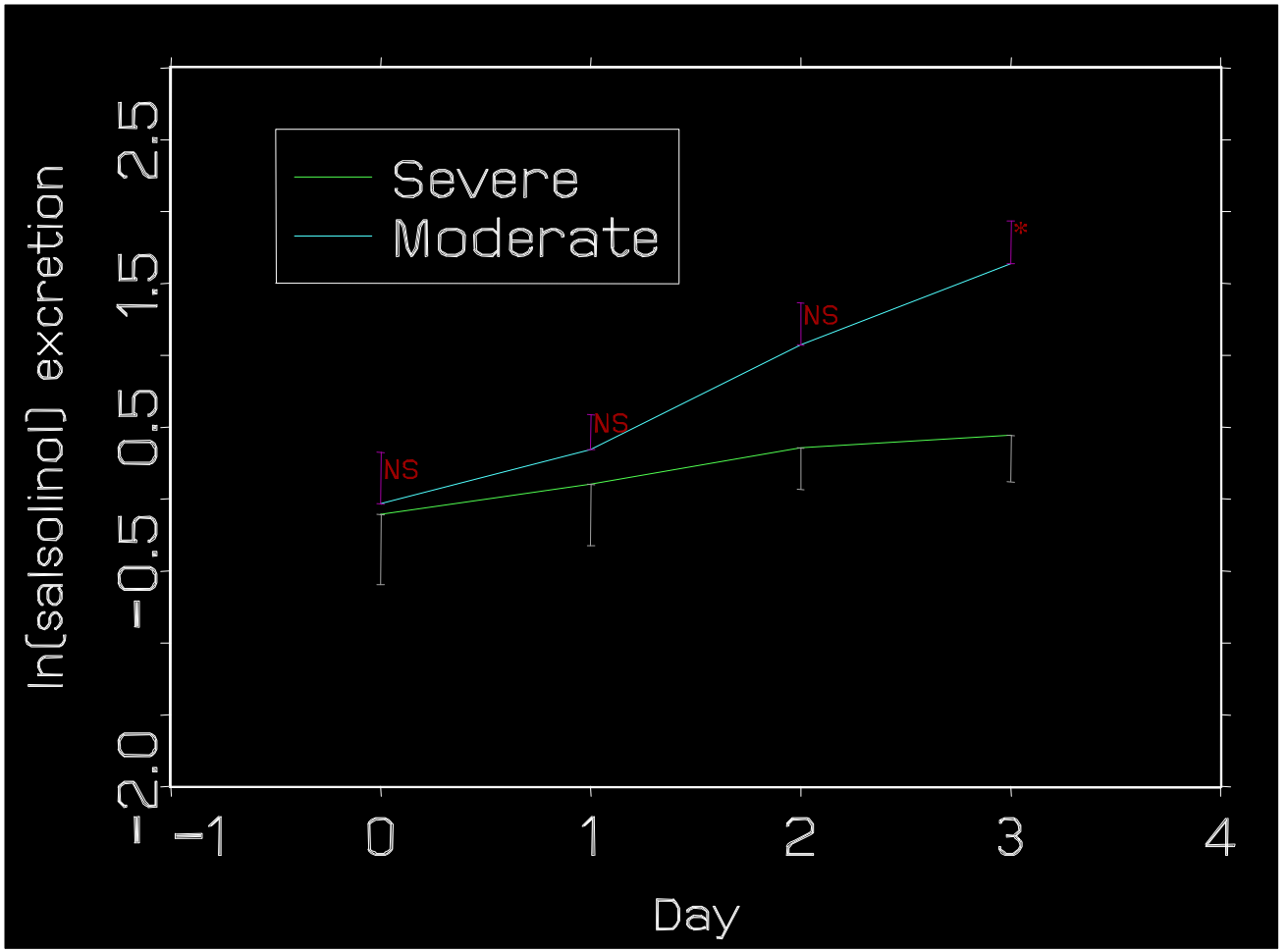
- Advantage:
  - May be the only design that answers questions of interest
- Diasadvantages:
  - Analyses can be difficult
  - Can be biased due to dropouts, especially if dropout related to treatment being studied

Measurements over time

- Important to consider individual subject profiles over time.
- Ignoring individual subjects can give misleading impression of
  - variation
  - direction of effects

Ignoring individual patients can misrepresent variation

Modified data from Crowder and Hand. Analysis of Repeated Measures



Ignoring individual patients can misrepresent variation

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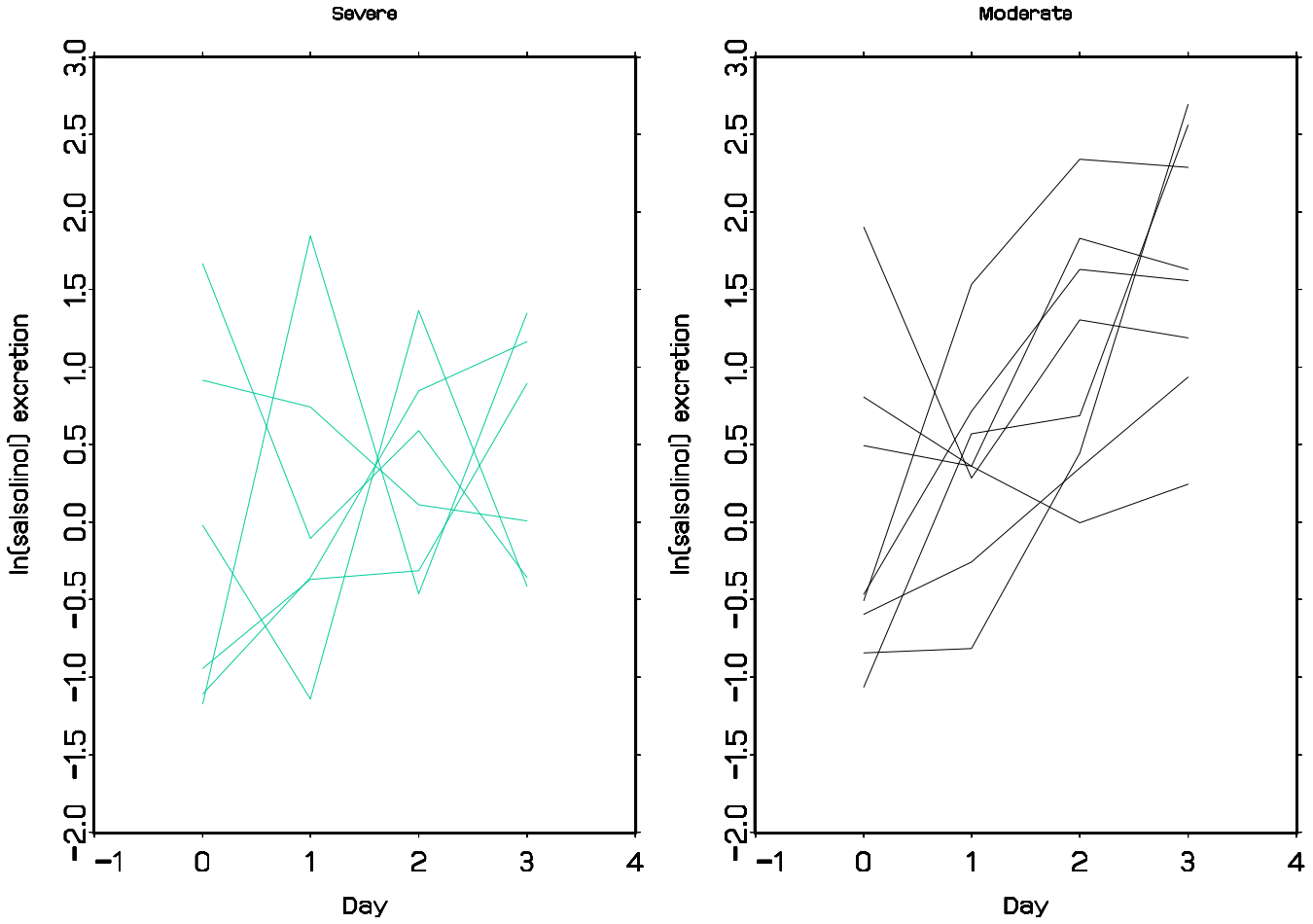
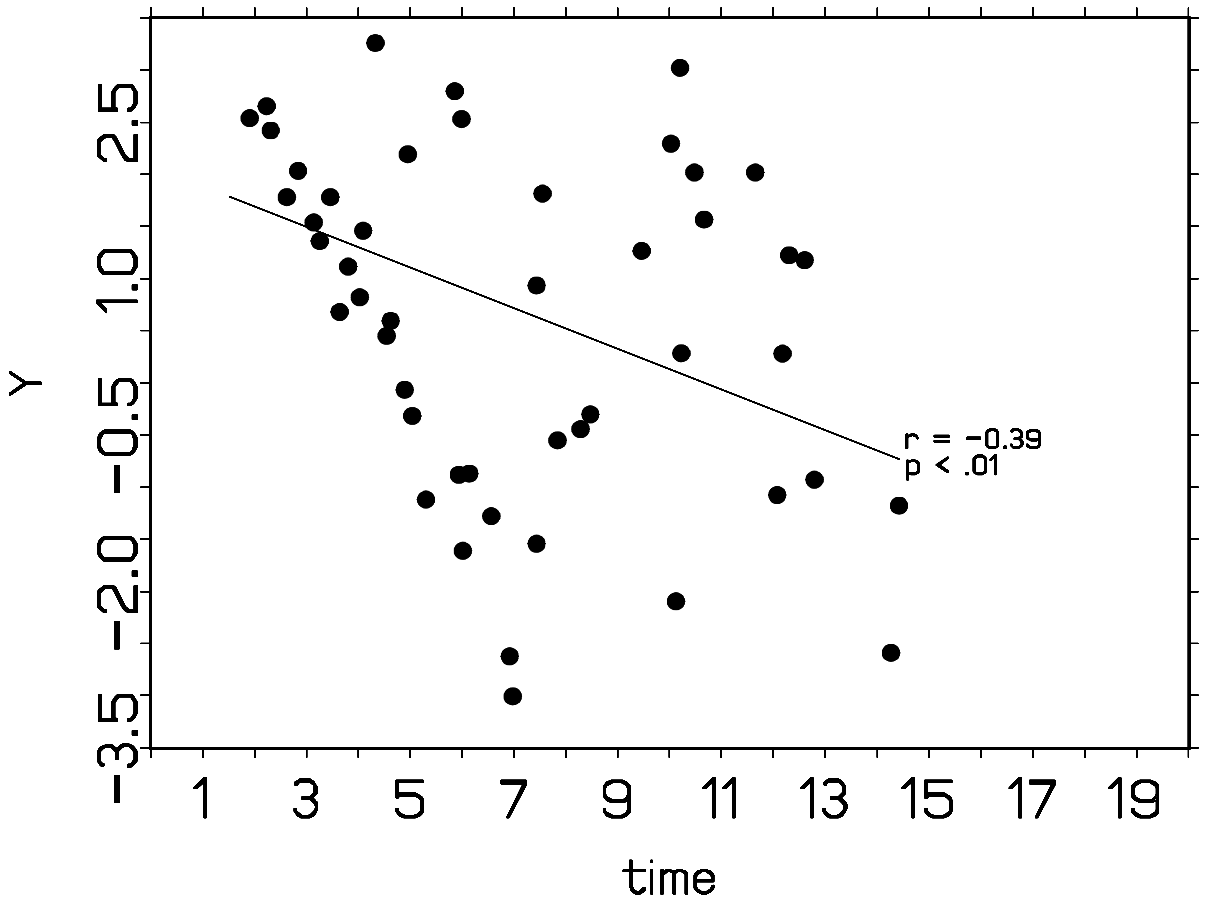


Ignoring individual patients can misrepresent direction of effects



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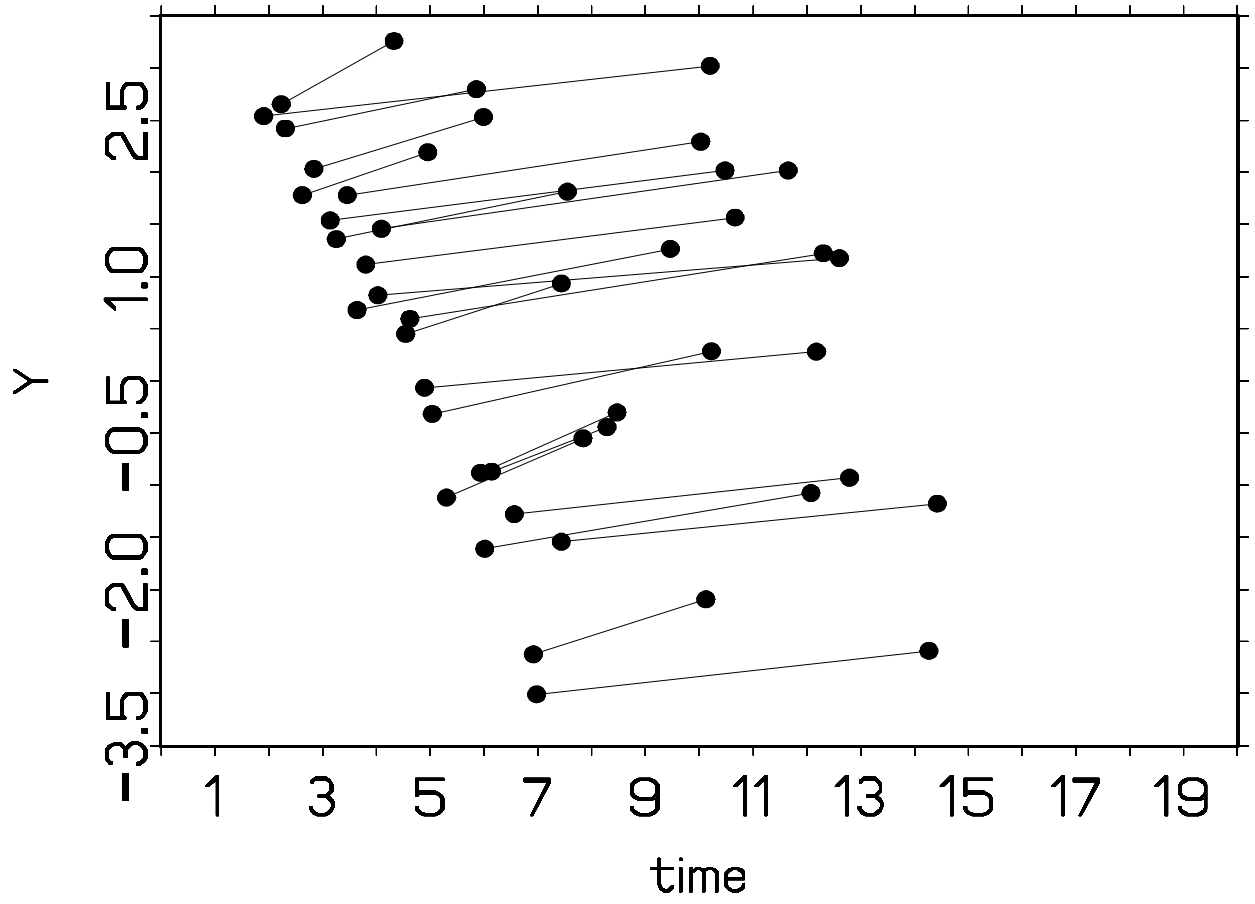
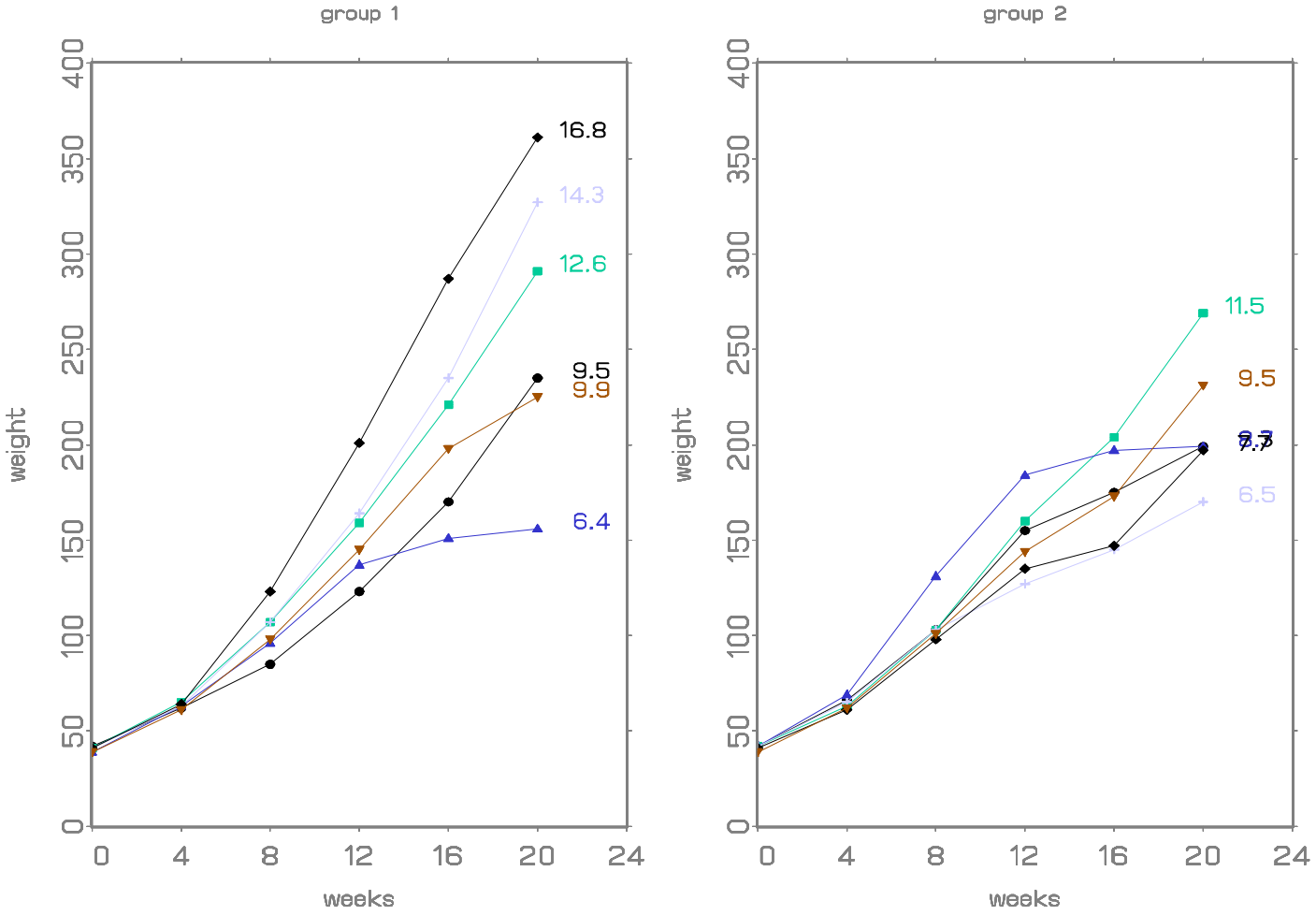


Analysis by summary measures

- Matthews et al recommend analysis by *summary measure*
- Common summary measures are
  - individual slopes
  - area under curve

Example of Analysis by individual slopes.

Data from Crowder and Hand



Example of Analysis by individual slopes.

Data from Crowder and Hand

Group 1	Group 2
9.5	8.3
12.6	11.5
6.4	8.7
14.3	6.5
16.8	7.7
9.9	9.5

Analyze this as a standard 2 group problem.

Analysis by summary measures.

Senn, BMJ, 1990

- Advantages
  - Easy
  - Summary measures may have an interpretation
- Disadvantages
  - Makes sense with different lengths of follow-up?
  - Effect of predictors measured at time points within subject?
  - Can a single summary measure can capture entire curve?

Handling dropouts in longitudinal studies

- Possible approaches.
- Analyze only those who complete therapy.
  - May bias results, especially if reason for dropout is related to outcome

Handling dropouts in longitudinal studies

- Use ``Last Observation Carried Forward (LOCF)'' method.
  - After patient has withdrawn, use the last observation.
  - Could bias results; last observation may not reflect true state of subject
  - Does not provide reasonable assessment of uncertainty
  - Generally dismissed as a method for handling dropouts

Handling dropouts in longitudinal studies

- Modeling the dropout process
  - Requires assumptions and sophisticated modeling methods.

- No generally accepted method for handling dropouts.