Assessing the Similarity of Bio-analytical Methods (Linear Case)

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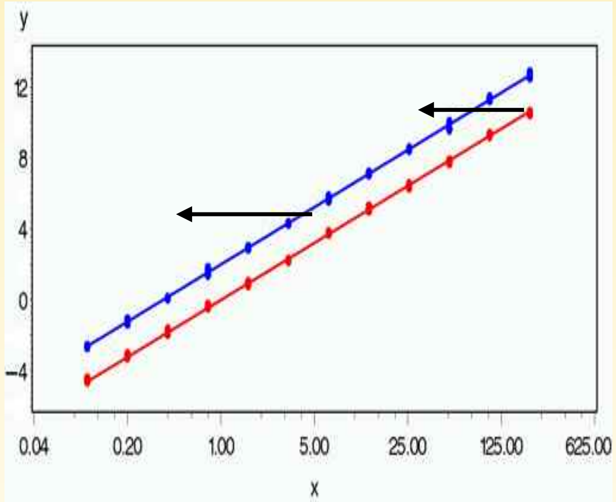
Outline

- Introduction
- Existing methods & potential problems
- New method
- Simulation study
- Summary and discussion

Introduction

- Why Similarity
  - A key assumption
  - RP

- Definition of similarity
  - Mathematically : **f (x)=g (px)**
  - Parallelism
  - P: relative potency.



Introduction (cont.)

- Target: Sufficiently Similar → Single RP

- Assessing the Similarity
  - Mathematically.

  - The assessment of the degree of similarity is very tricky between two sparse, noisy sets of non-linear dose response data sets.

  - No universal Strategy

  - Two kinds of existing method:
    (1) Significance Test
    (2) Equivalence Test.

Significance Test

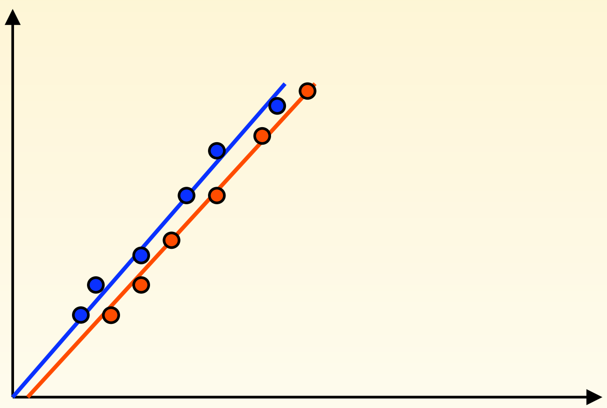
(linear case: Similarity⇔ Same Slopes)

- Significance Test

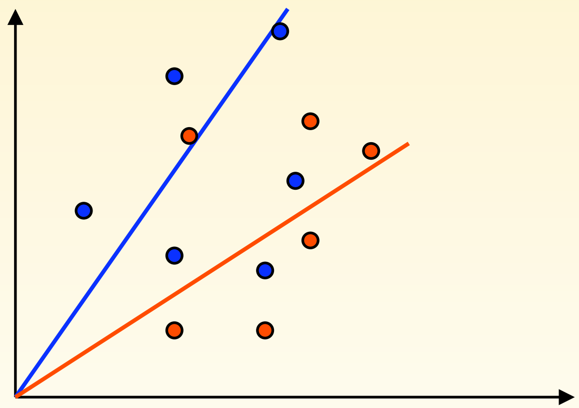
  Ho: Two slopes are exactly same.

  Ha: Two slopes are different;

When the precision increases....



Lab A: Good Precision
→ Not similar



Lab B: Poor Precision
→Similar

Equivalence Test

(linear case: Similarity= Same Slopes)

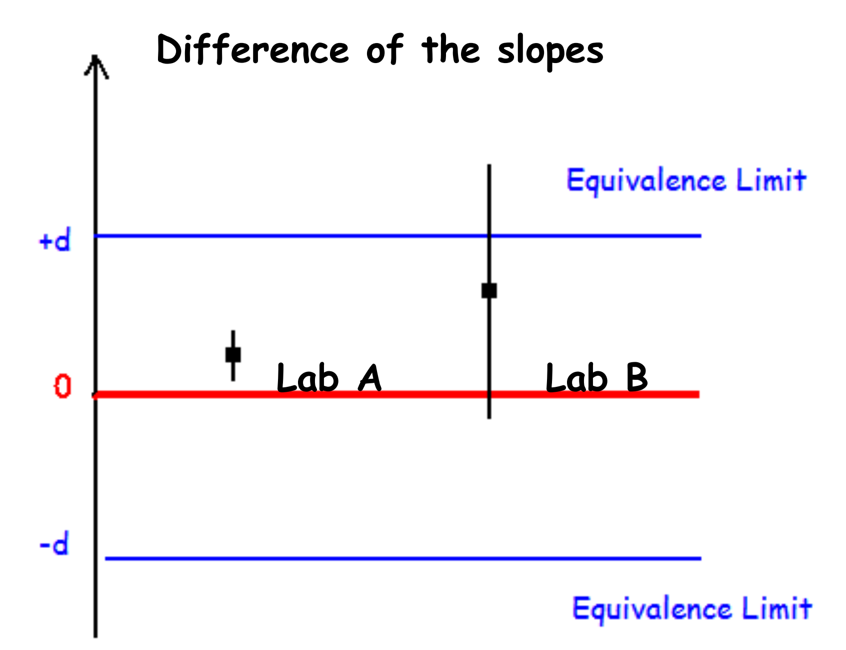
- Equivalence test

Ho: |difference| >=D Ha: |difference| <D

- The equivalence limits define differences between test and standard preparations that are considered unimportant.
  - Step1: CI for difference
  - Step2: CI vs. Equivalence limit

Equivalence Test

(linear case: Similarity= Same Slopes)



	Lab A	Lab B
Significance test	Not similar	Similar
Equivalence Test	Similar	Not Similar

Equivalence Test

(linear case: Similarity= Same Slopes)

- Fixed equivalence limit (Not vary with application)
  - **[0.8,1.25]** for the ratio of the slopes

- Capability based equivalence limit (Tolerance limit)
  - Manage the rate at which we falsely detect non-similarity
  - Can be assessed by evaluating reference material relative to itself.
    1. For complete reference data
    2. Pair them in all possible combination
    3. set up CI….
    4. use the most extreme boundary.

Equivalence Test

(linear case: Similarity= Same Slopes)

- DE (dilution effect)

$$DE=100\%(2^{1-bs/br}-1)<=20\%$$

  - A statistic called dilution effect was introduced in the industry to assess dilution similarity. (Schofield T. 2000).The dilution effect is a measure of the percent bias per 2-fold dilution in a test samples' value relative to that of the reference standard.
  - The absolute value of dilution effect less than 20% has been used in the industry to conclude dilution similarity (parallelism) between the test sample and the reference standard

New Method

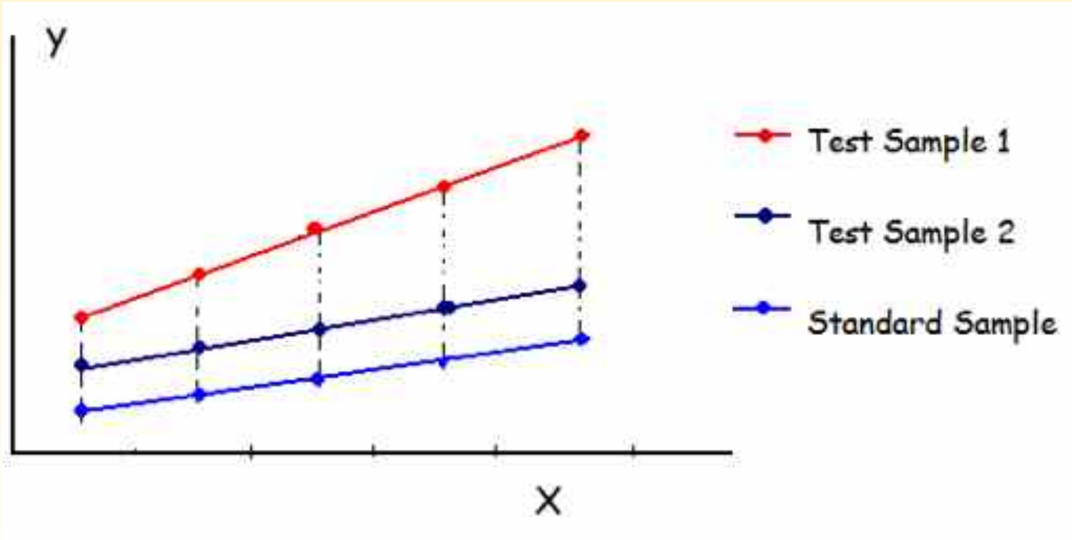
- Equivalence Test
- Overall difference of the response: shape of the curves

New Method: J-method

- J- method: $Y_{1i} - Y_{2i} \sim A_i + \omega_i \qquad \omega_i \sim N(0, \tau^2)$

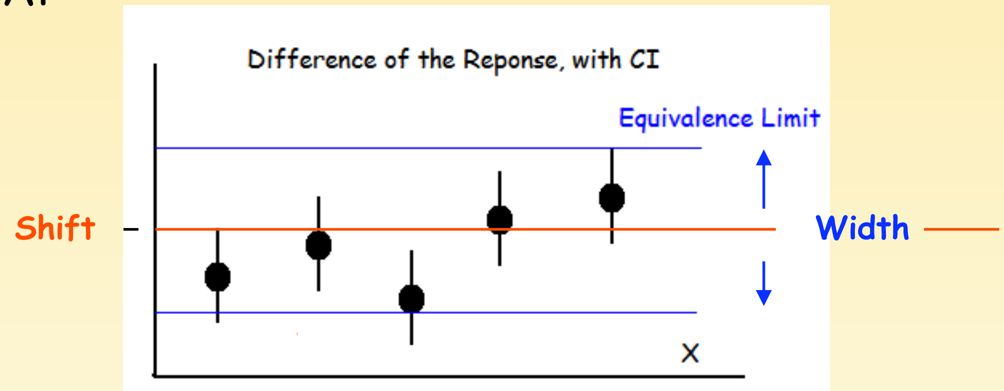
- Parallel ⇔ $A_1 = A_2 = \ldots. = A_5 = a_1 + b_1 x - (a_2 + b_2 x) = a_1 - a_2$

Considering variation....



New Method: J-method (cont.)

- Estimate the CI for Ai



- Construct Equivalence Limit

(1) Width-- Variation that are considered to be acceptable Standard curve compare to itself (Tolerance Limit)

(2) Shift-- $\hat{a}_1 - \hat{a}_2$

New Method: J-method modification (cont.)

- Deal with large variation

$$\log(y_1) - \log(y_2) = \log(y_1/y_2)$$

- Control the width of equivalence limit
  - 2-fold difference boundary

$$y_1/y_2 <= 2 \rightarrow \log(y_1) - \log(y_2) <= \log(2) \approx 0.7$$

$$y_1/y_2 >= 0.5 \rightarrow \log(y_1) - \log(y_2) >= \log(0.5) \approx -0.7$$

  - 3-fold difference boundary

$$y_1/y_2 <= 3 \rightarrow \log(y_1) - \log(y_2) <= \log(3) \approx 1.1$$

$$y_1/y_2 >= 1/3 \rightarrow \log(y_1) - \log(y_2) >= \log(1/3) \approx -1.1$$

Simulation Study

- Linear Case
  - F
  - DE
  - J, J2, J3

Simulation Settings

Test Sample $Y_i = a_1 + b_1 X_i + \varepsilon_i$

Standard Sample $Y_i = a_2 + b_2 X_i + \delta_i$

$\varepsilon_i \sim N(0, \sigma^2)$ $\delta_i \sim N(0, \sigma^2)$

$X_i = \log(1,2,4,8,16)$ 2 fold dilution (16 to 1)

$a_1 = a_2 = 1$

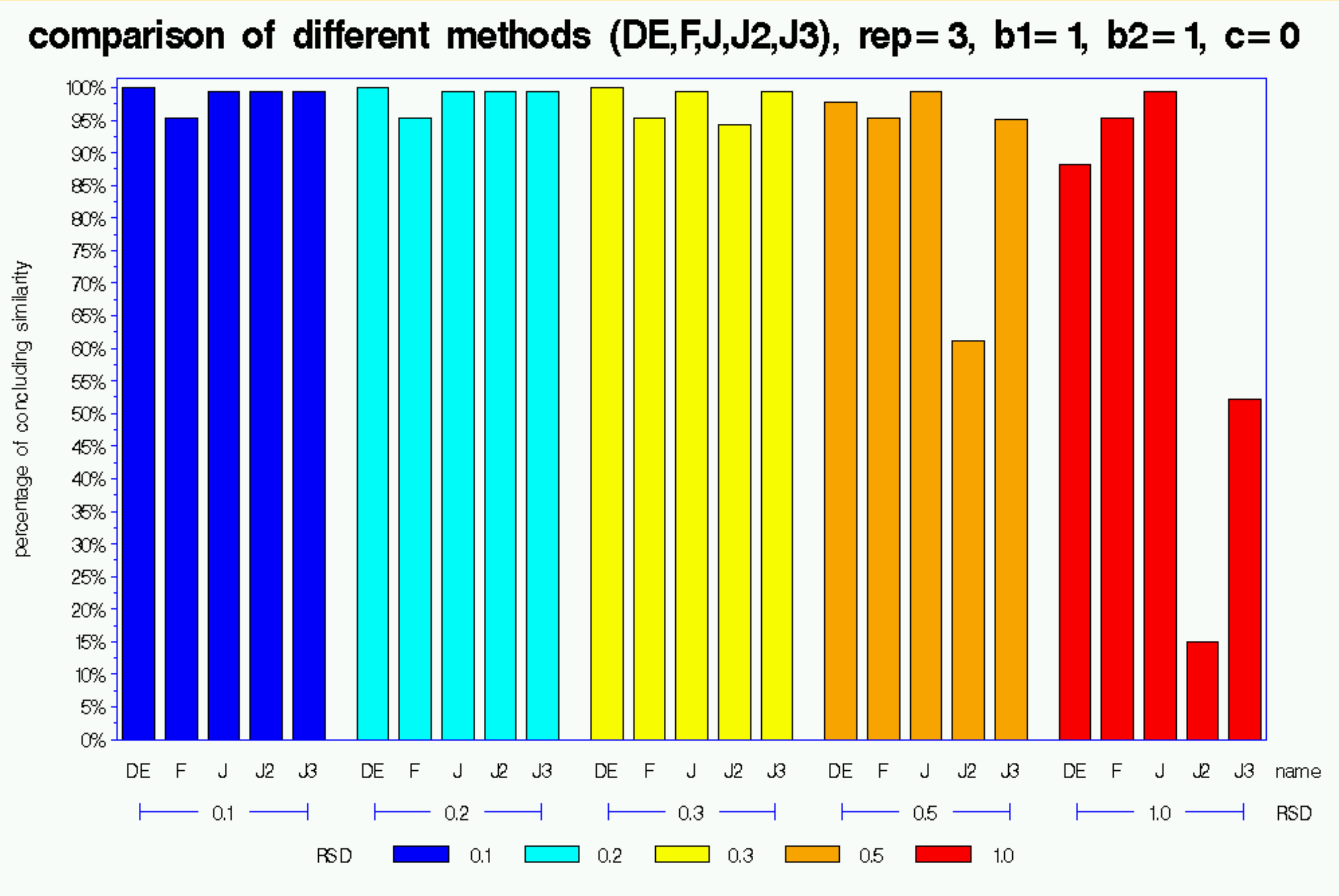
$b_2 = 1$

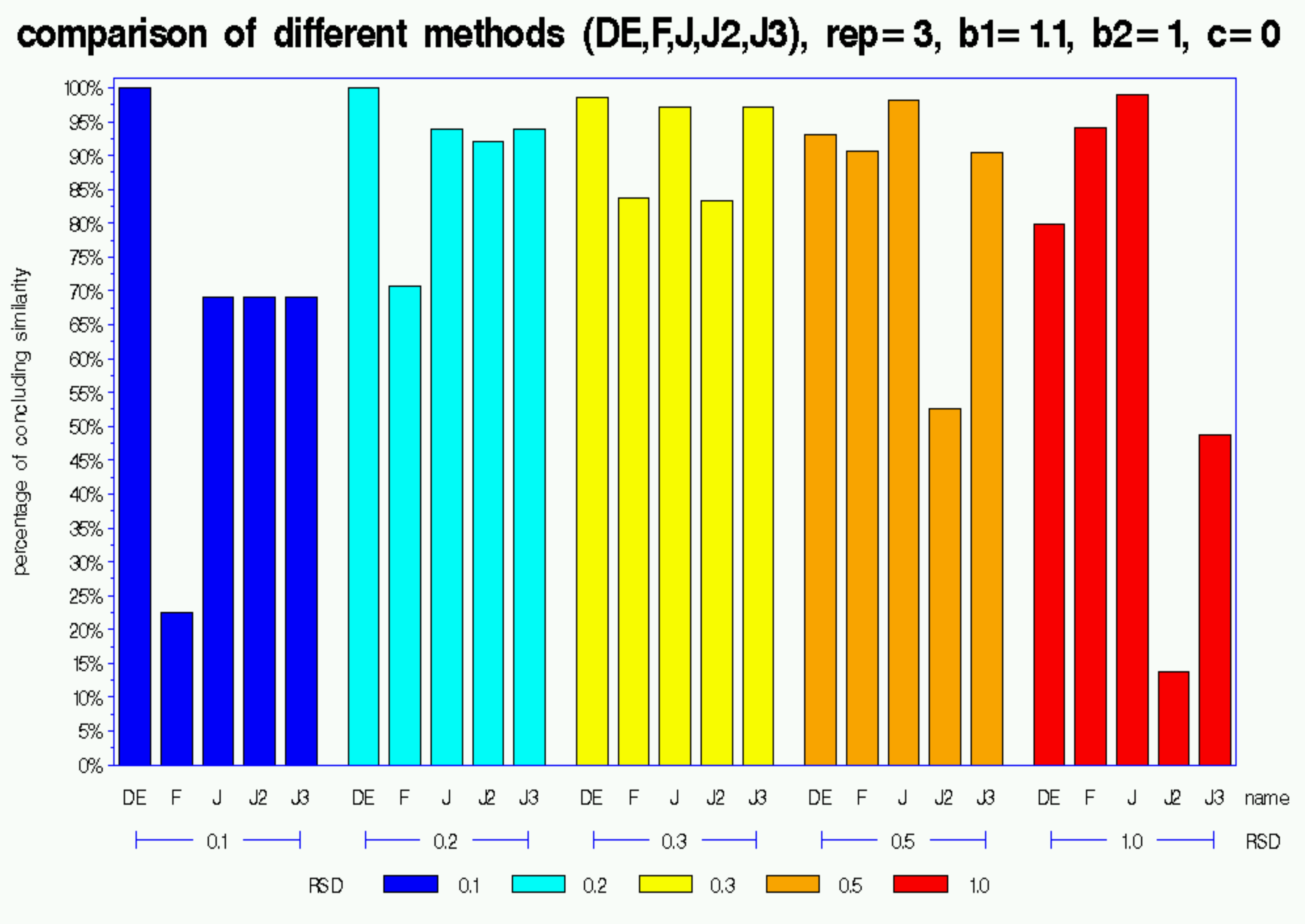
$b_1 = 1,\ 1.01,\ 1.1,\ 1.3,\ 1.5,\ 2$

$RSD = 5\%, 10\%, 20\%, 30\%, 50\%, 100\%$

3 Replicates

numbers of simulation = 1000 for each parameter setting


comparison of different methods (DE,F,J,J2,J3), rep=3, b1=1, b2=1, c=0
percentage of concluding similarity
100%
95%
90%
85%
80%
75%
70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
DE F J J2 J3 DE F J J2 J3 DE F J J2 J3 DE F J J2 J3 DE F J J2 J3 name
0.1 0.2 0.3 0.5 1.0 RSD
RSD 0.1 0.2 0.3 0.5 1.0



comparison of different methods (DE,F,J,J2,J3), rep=3, b1=1.1, b2=1, c=0
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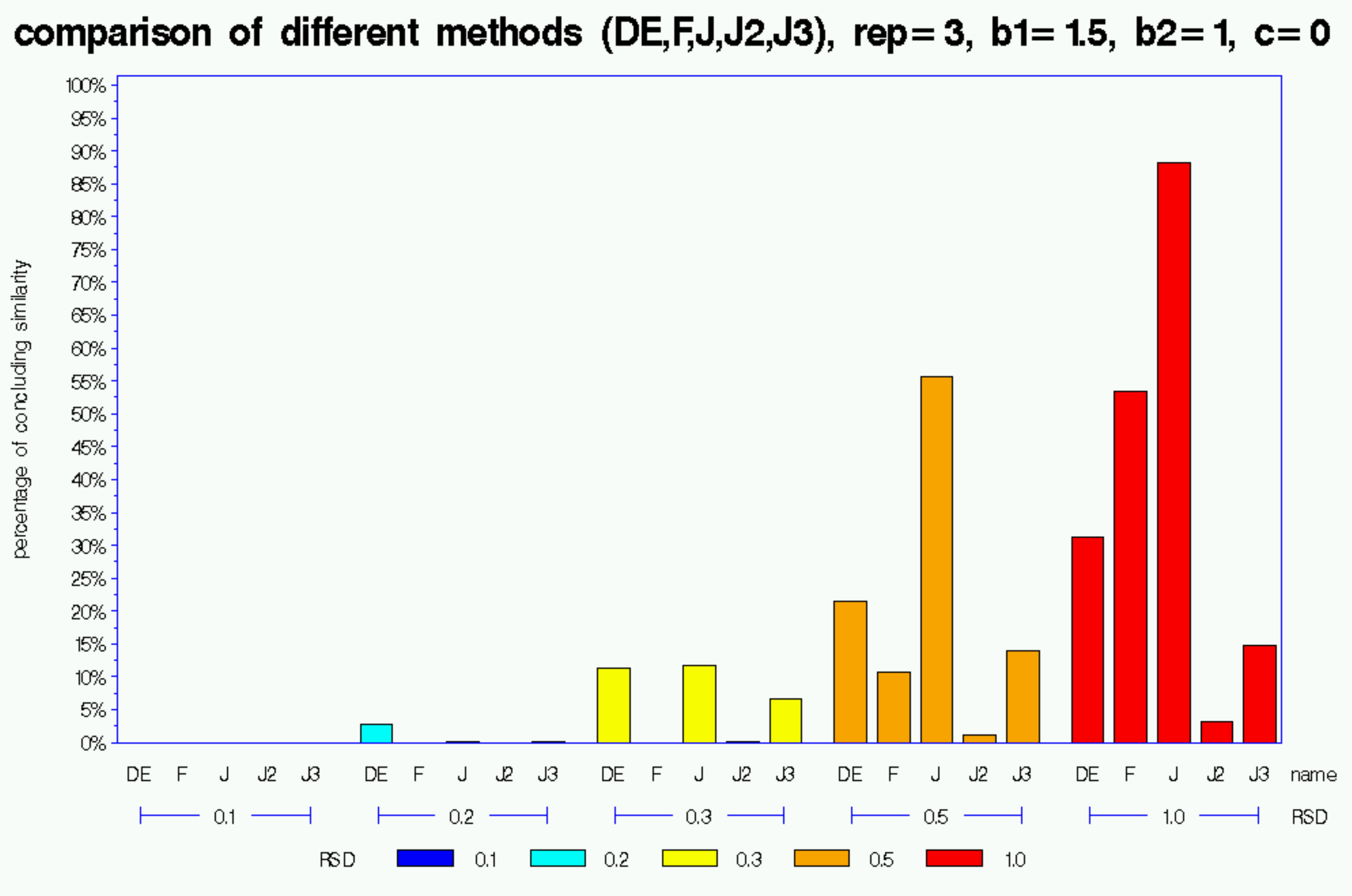

comparison of different methods (DE,F,J,J2,J3), rep=3, b1=1.5, b2=1, c=0
percentage of concluding similarity
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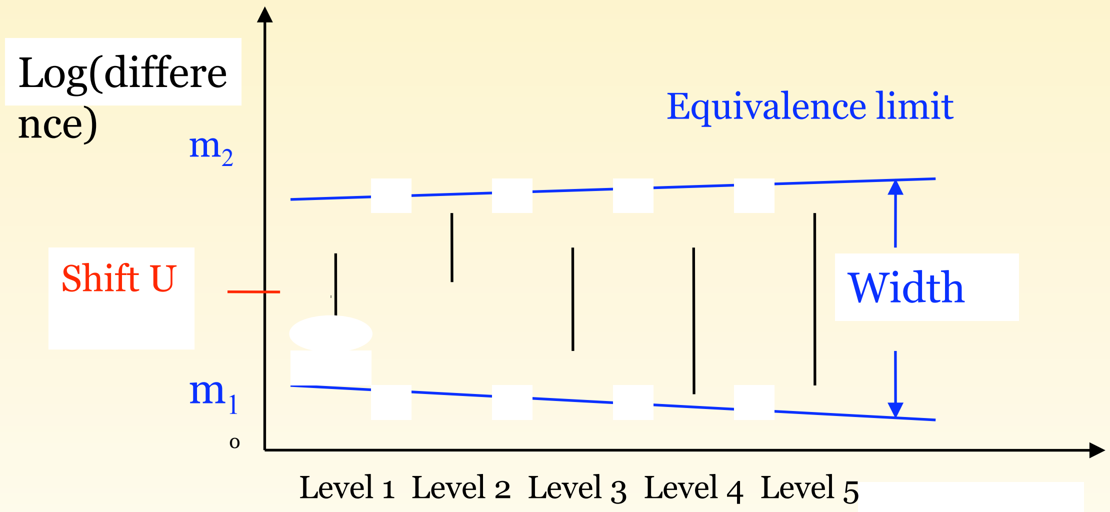
RSD 0.1 0.2 0.3 0.5 1.0

Summary

- F: variance ↗, tends to conclude parallel
- DE: variance ↗, may not be able to get the right conclusion
- J, J2, J3: J3 works well, even when variance ↗

Discussion

- Heterogeneous Variance: $Var(y) = c \cdot (y)^{2r}$
  - New method can be easily applied



Thank You