BOOTSTRAPPING & DISSOLUTION SIMILARITY: Q&A

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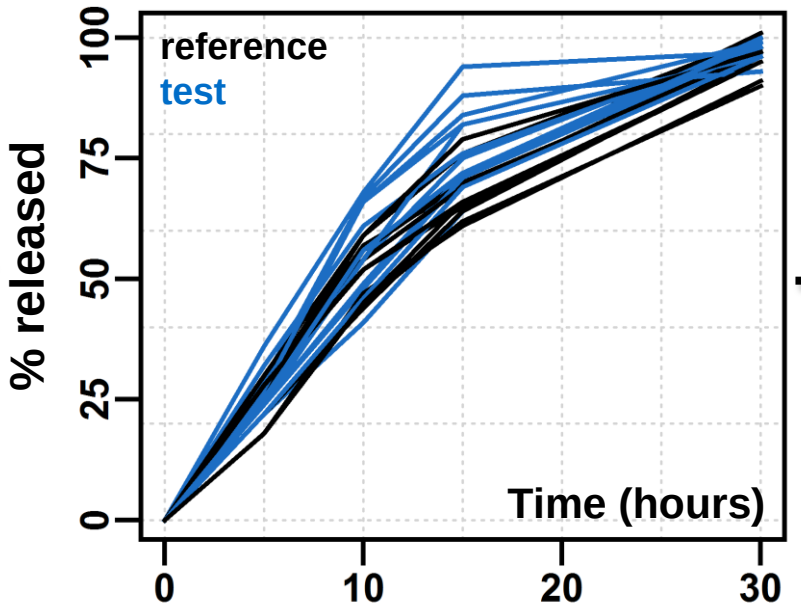
SIMILARITY: CLAIM OF EQUIVALENCE

Test	Reference
Test A	Test B
Biobatch	Biobatch
Pilot	Clinical
Strength 1	Strength 2
API 1	API 2
+Excipient	−Excipient
Site 1	Site 2

...



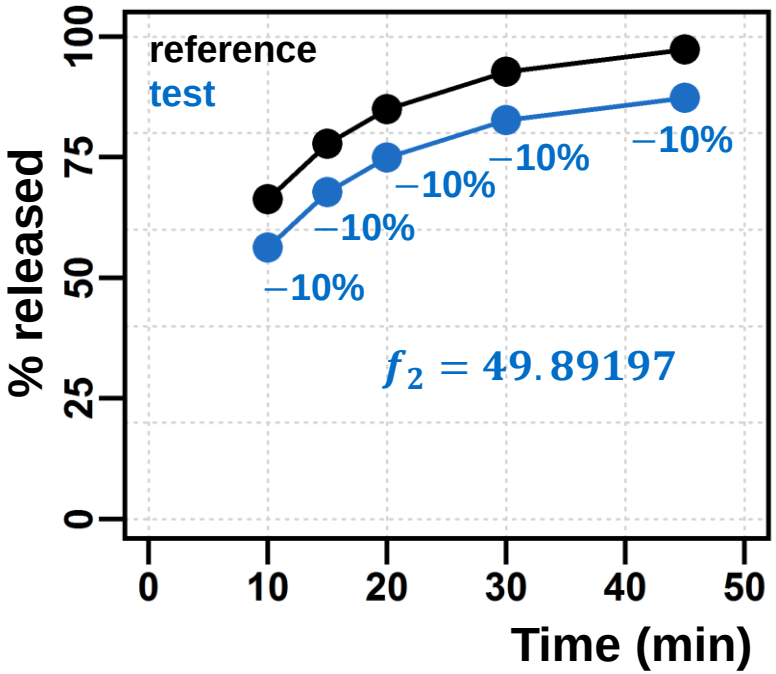
Type
(M)ANOVA
f1(2)
Bayesian
MD
Bootstrap
MSD
T^2 test
EDNE test
PCA

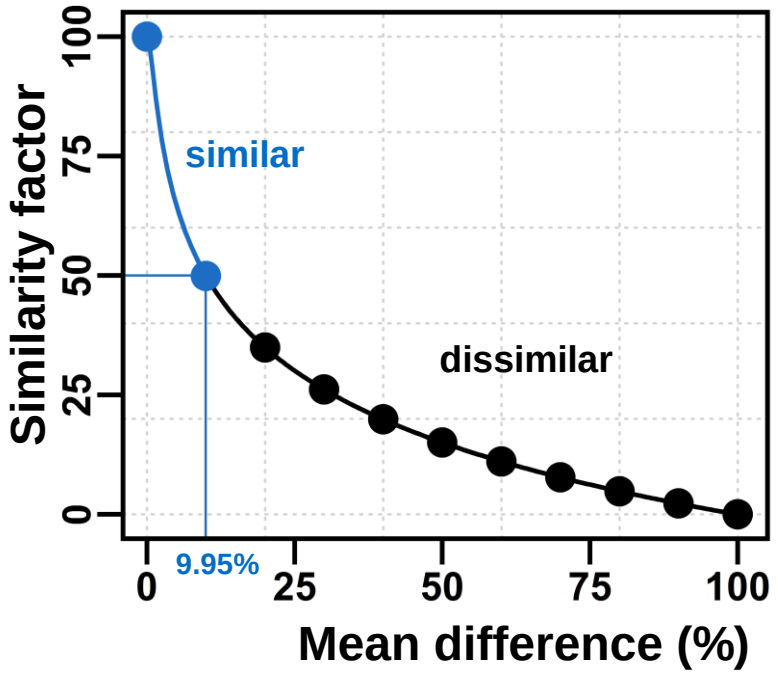
...

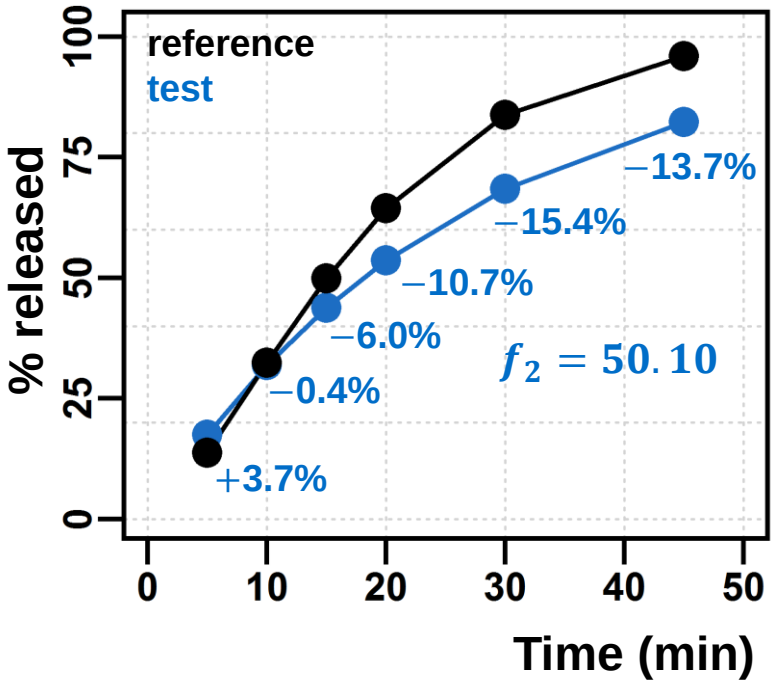
(M)ANOVA (multivariate) analysis of variance; f1(2) similarity factor; MD maximum deviation; MSD multivariate statistical distance; EDNE Euclidean distance of the nonstandardized expected (values); PCA principal component analysis

FIT FACTOR: MOORE & FLANNER

$$f_2 = 50\ log\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n}(\boldsymbol{R_t} - \boldsymbol{T_t})^2\right]^{-0.5} \times 100\right\}$$







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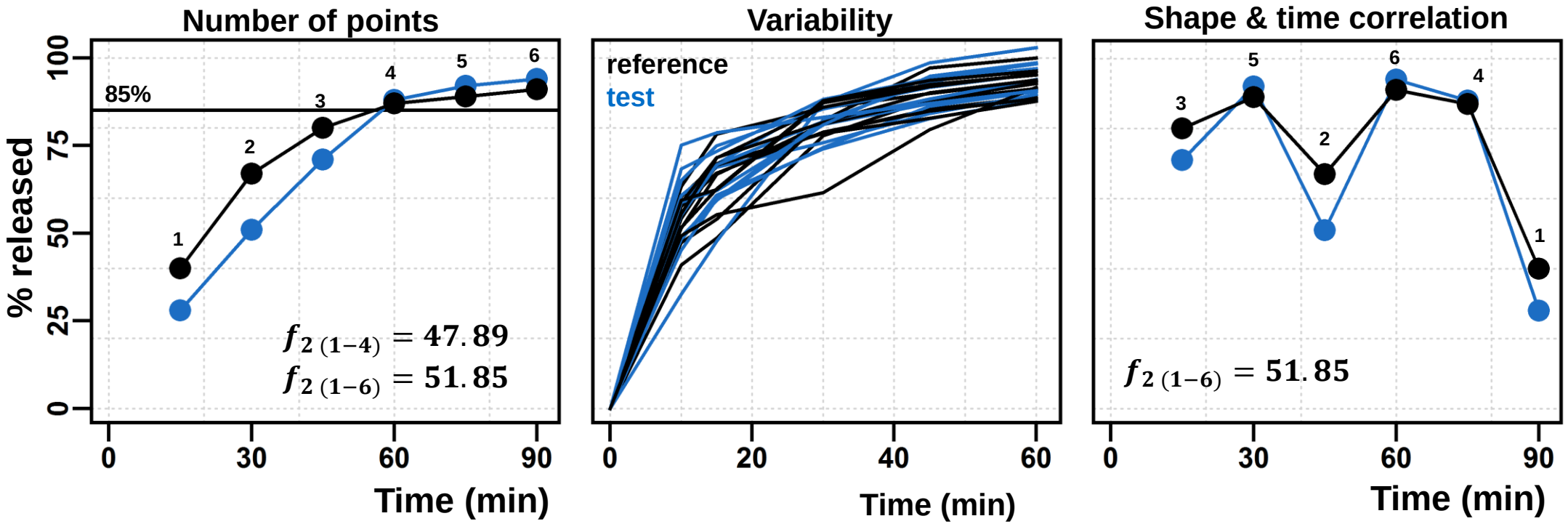
Moore & Flanner (1996). Pharm Technol 20(6): 64-74

SIMILARITY FACTOR: WHAT'S WRONG WITH YOU?

$$f_2 = 50\ log\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n}(\boldsymbol{R_t} - \boldsymbol{T_t})^2\right]^{-0.5} \times 100\right\}$$



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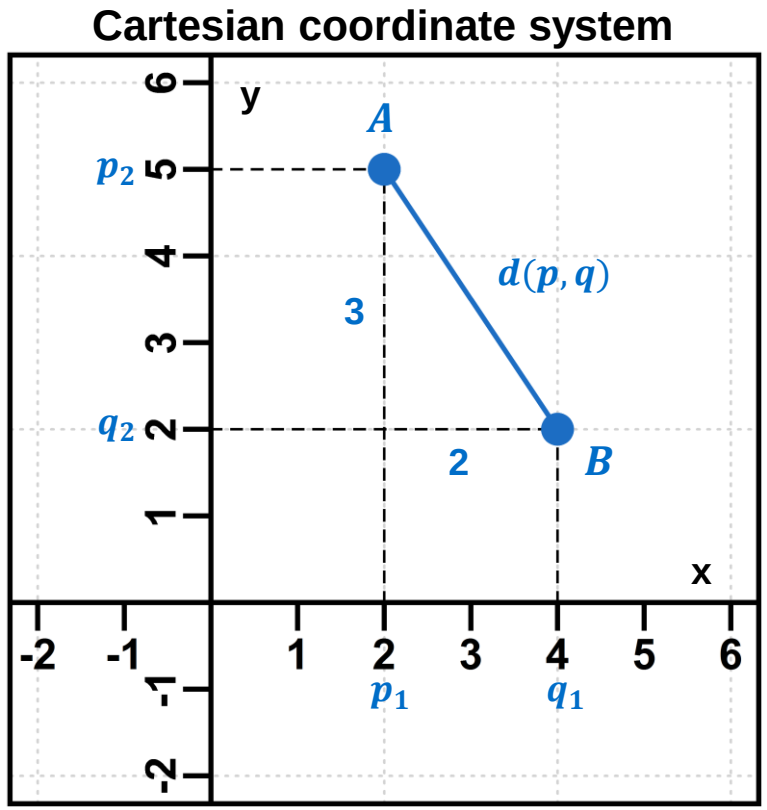
STATISTICIANS: VIEW ON SIMILARITY FACTOR

(…) **impossible to evaluate false positive or false negative** (…). (…) **too liberal in concluding similarity.**

Liu et al. (1997). Drug Info J. 31: 1255-1271

(…) f_2 (…) **series of monotone** (…) **transformations of the Euclidean distance,** (…) **procedure where neither the type I error rate nor power can be controlled and which really hurts a statistician‘s soul.**

Hoffelder (2019). Biom J. 61(5): 1120-1137



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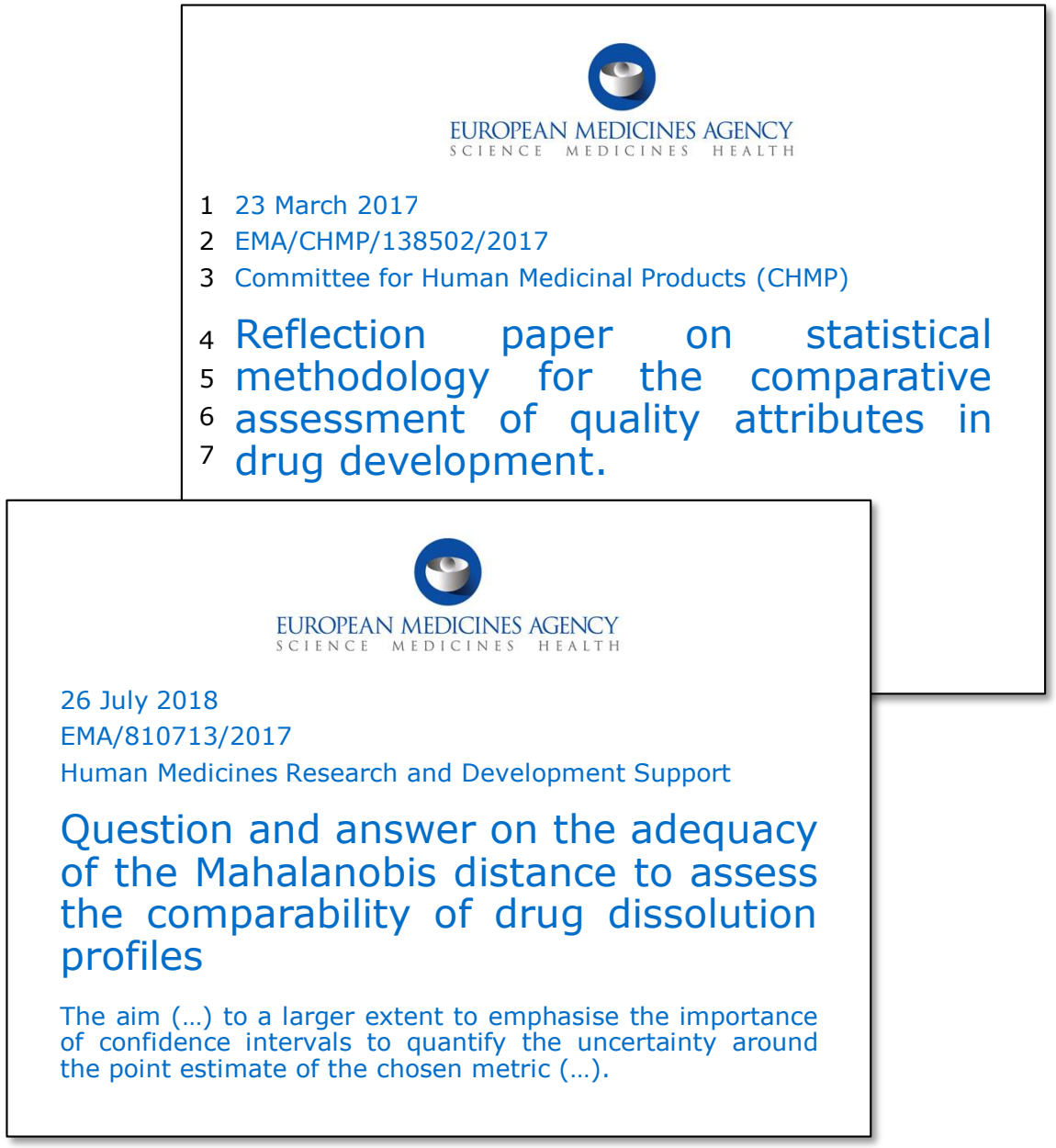
EMA: REFLECTIONS

[6.3] **The f2 (…) unfavorable statistical properties (…), no (…) quantification of the risk to false positively conclude on similar dissolution is possible.**

[Answer:] (…) **is based only upon the (…) numerical value for f2 (point estimate ≥ 50). (…) uncertainty related to the f2 sampling distribution is not accounted for.**



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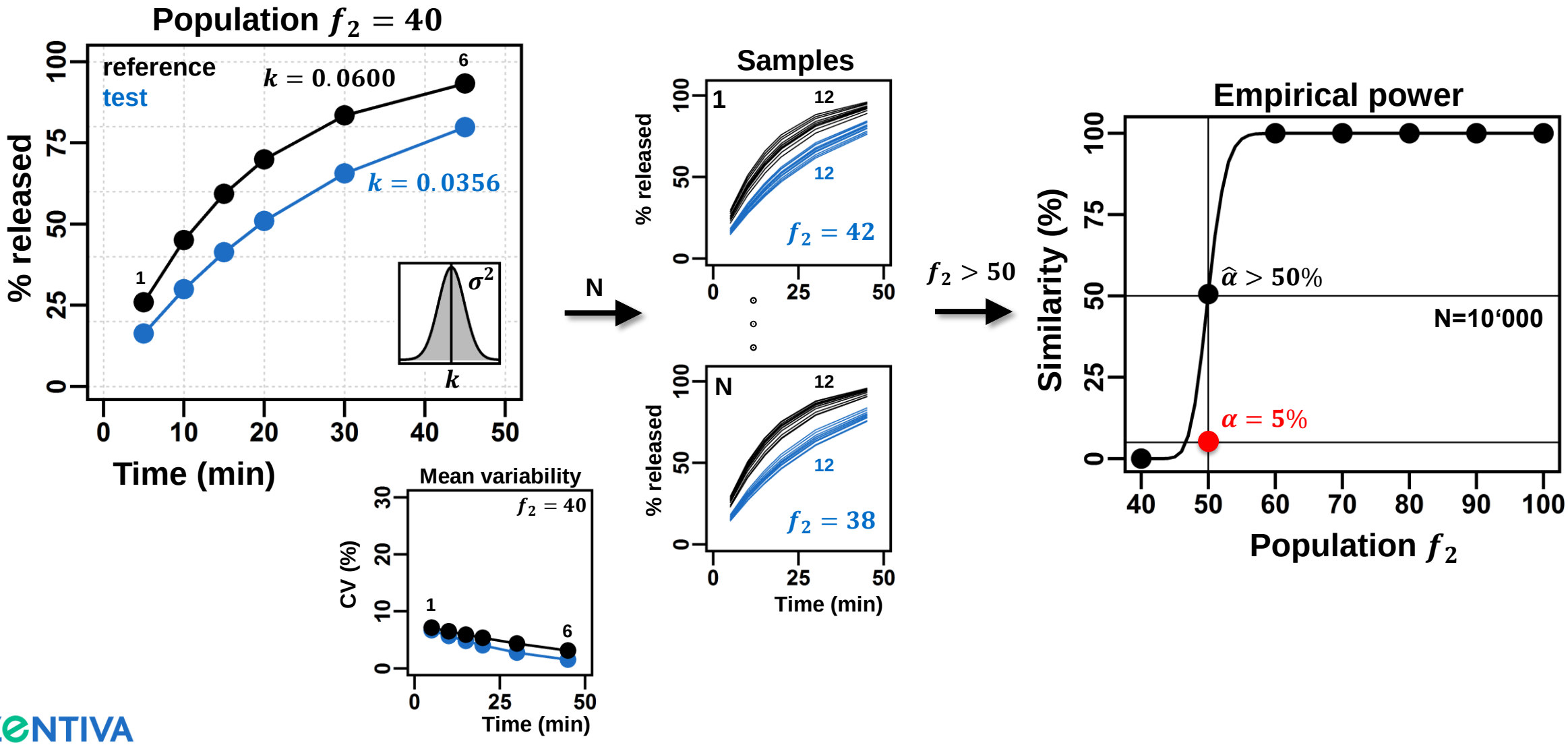
DISSOLUTION SIMULATION: $y = 100 \times \left(1 - e^{-kt}\right)$



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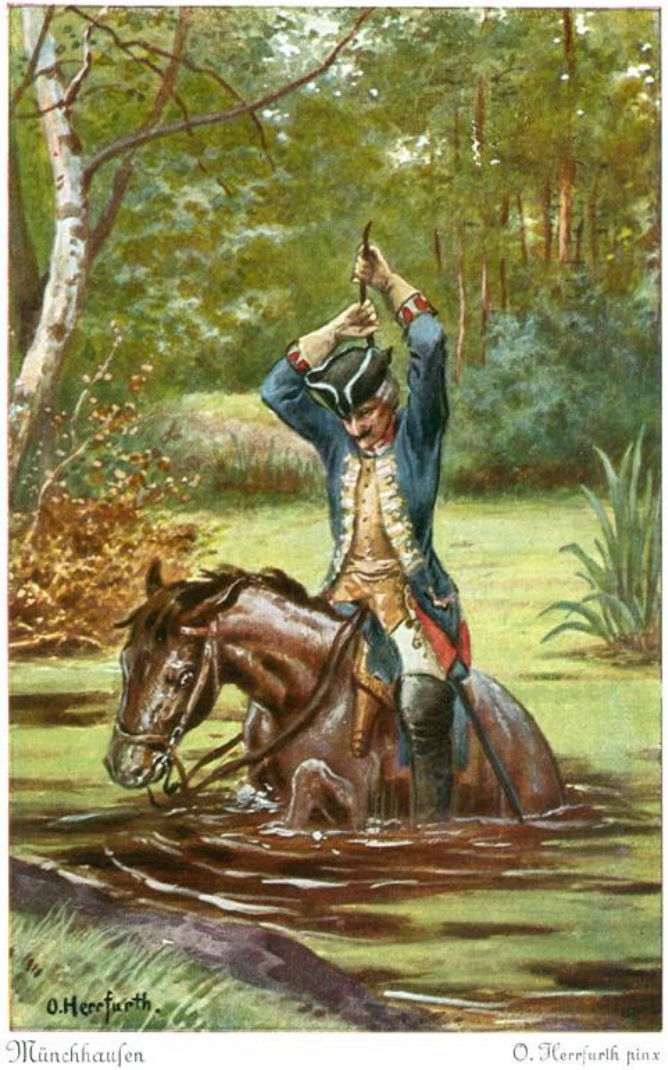
EMA Q&A: BOOTSTRAP

[Answer:] (…) **bootstrap methodology could be used to derive confidence intervals for f2** (…), (…) **the preferred method over f2 and MD.** **EMA/810713/2017**

boot·strap /ˈbu:tstræp/ *noun* IDM **pull *I* drag yourself up by your (own) bootstraps** *(informal)* **to improve your situation yourself, without help from other people**

Oxford Advanced Learner‘s Dictionary of Current English (2000). Oxford University Press



Raspe (1785): Baron Munchausen's Narrative of his Marvellous Travels and Campaigns in Russia

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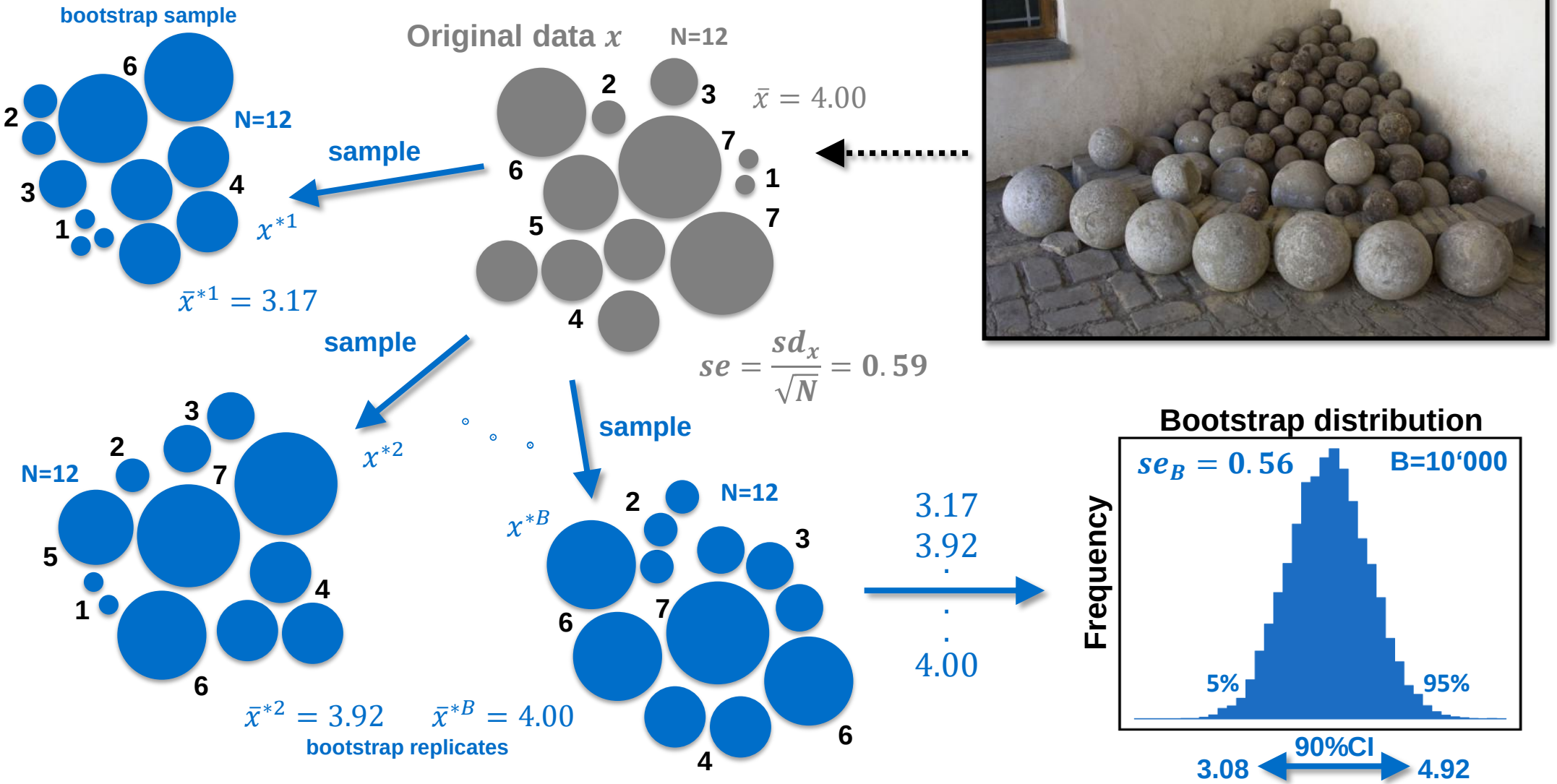
BOOTSTRAPPING: PRINCIPLE



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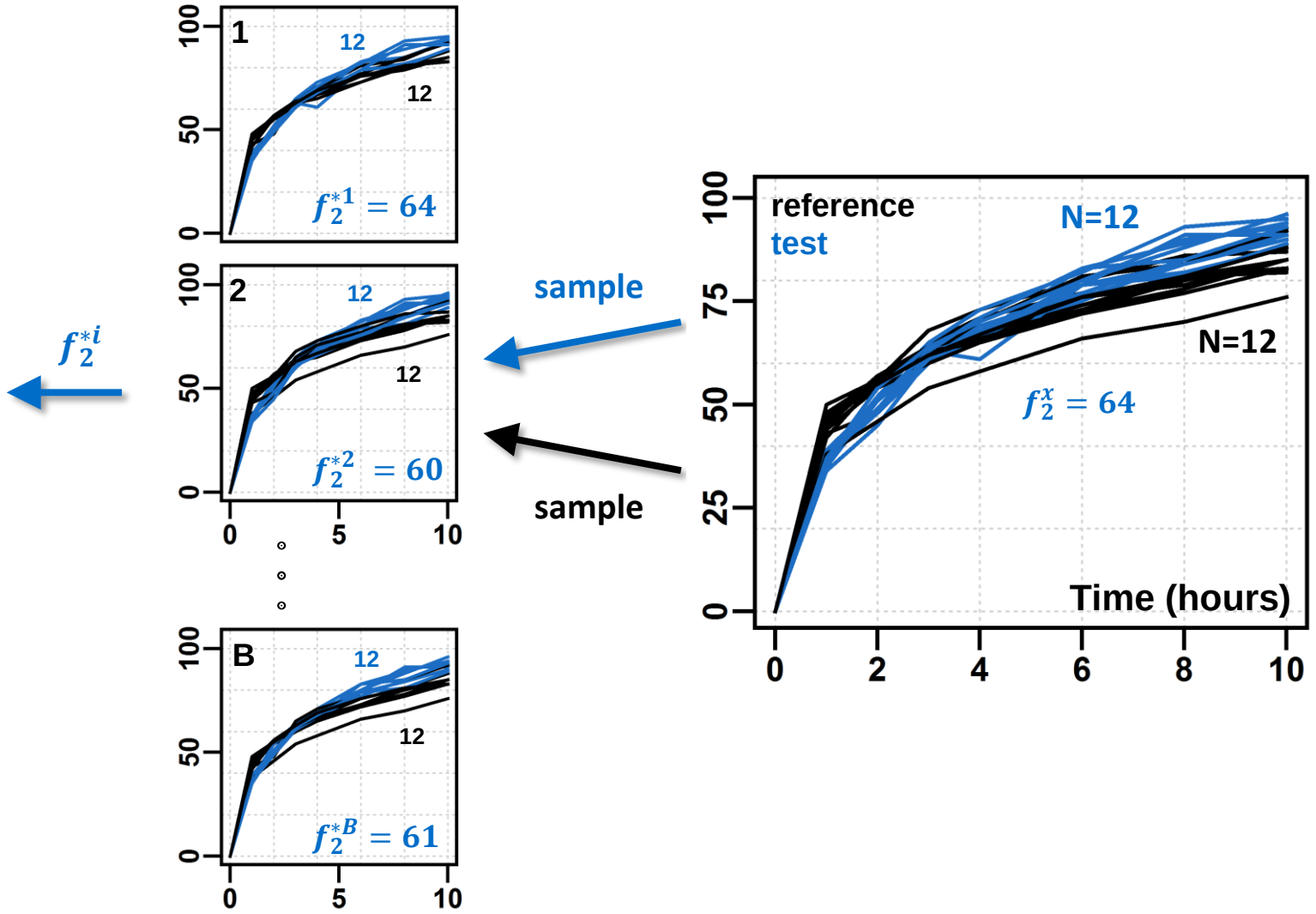
BOOTSTRAPPING DISSOLUTION: CI

90% bootstrap CI[1]		
Type	**Lower**	**Upper**
Normal	60.2217	66.9493
Percentile	59.8591	66.5973
Basic	60.5737	67.3119
BC	60.6481	67.4051
BCa	60.7555	67.5536
Bootstrap-*t*[2]	60.5844	67.8099

[1]R (v3.6.1); B0=10‘000; [2]B1=1‘000; BC bias-corrected; BCa bias-corrected and accelerated.

Similarity (...) be declared if the CI for f2 (…) entirely above 50.
EMA/810713/2017



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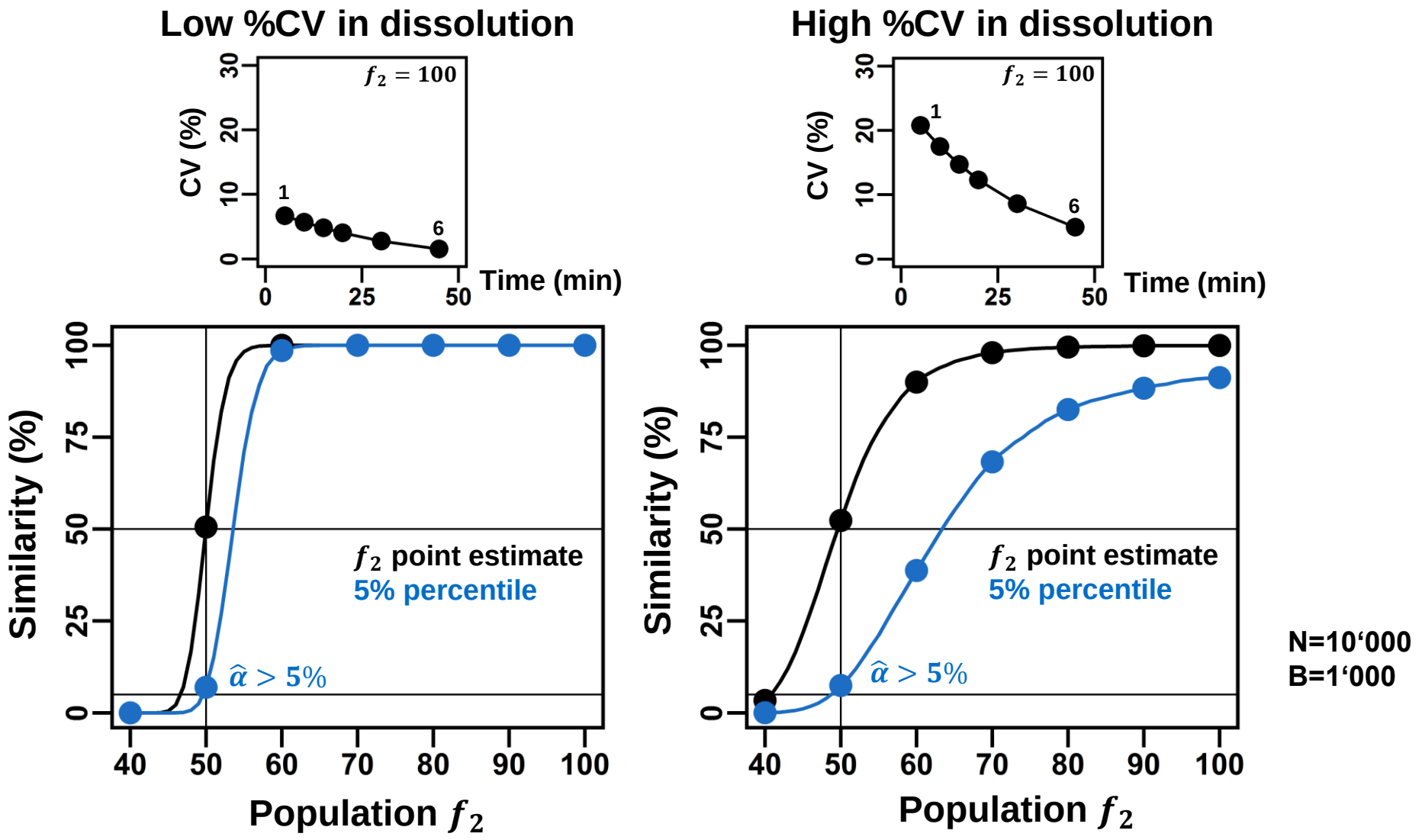
BOOTSTRAPPING DISSOLUTION: ALL EASY?

90% bootstrap CI[1] (data I)		
Type	Lower	Upper
Normal	75.3720	105.6605
Percentile	62.7877	92.9877
Basic	88.0448	118.2448
BC	87.4104	99.7090
BCa	87.4081	99.7060
Bootstrap-*t*[2]	87.9071	123.3391
[1]R (v3.6.1); B0=10‘000; [2]B1=1‘000		

90% bootstrap CI[1] (data II)		
Type	Lower	Upper
Normal	49.0571	65.8814
Percentile	50.5090	67.4505
Basic	47.4880	64.4295
BC	50.4077	67.3106
BCa	49.9249	66.4951
Bootstrap-*t*[2]	47.5351	66.7653
[1]R (v3.6.1); B0=10‘000; [2]B1=1‘000		

BOOTSTRAPPING DISSOLUTION: ALPHA & POWER



N=10‘000
B=1‘000

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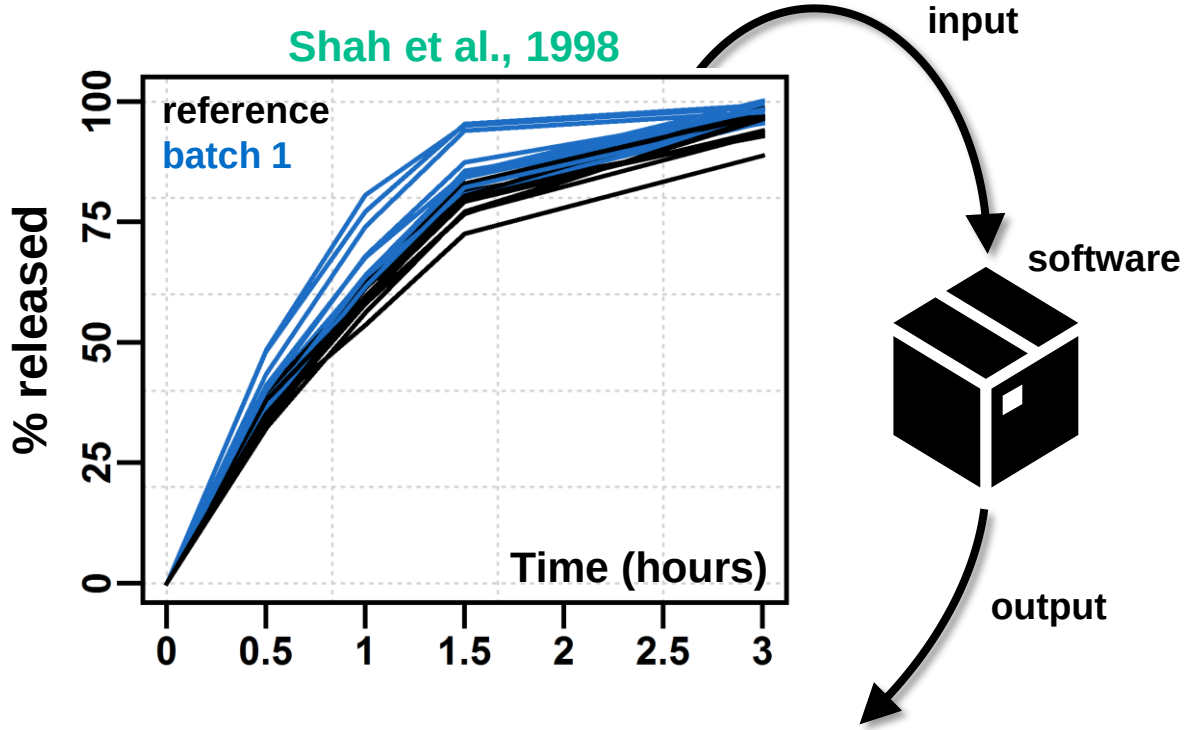
BOOTSTRAP IN PRACTICE: DL

[Major objection] **Biowaiver** (…) **may not be sufficiently supported** (…). (…) **90% confidence interval of the f2 similarity factor calculated by bootstrapping** (…). **The output should include at least the number of bootstraps, the 5%, 50%** (median) **and 95% percentiles. Evidence that the statistical software has been validated should be provided as well.**

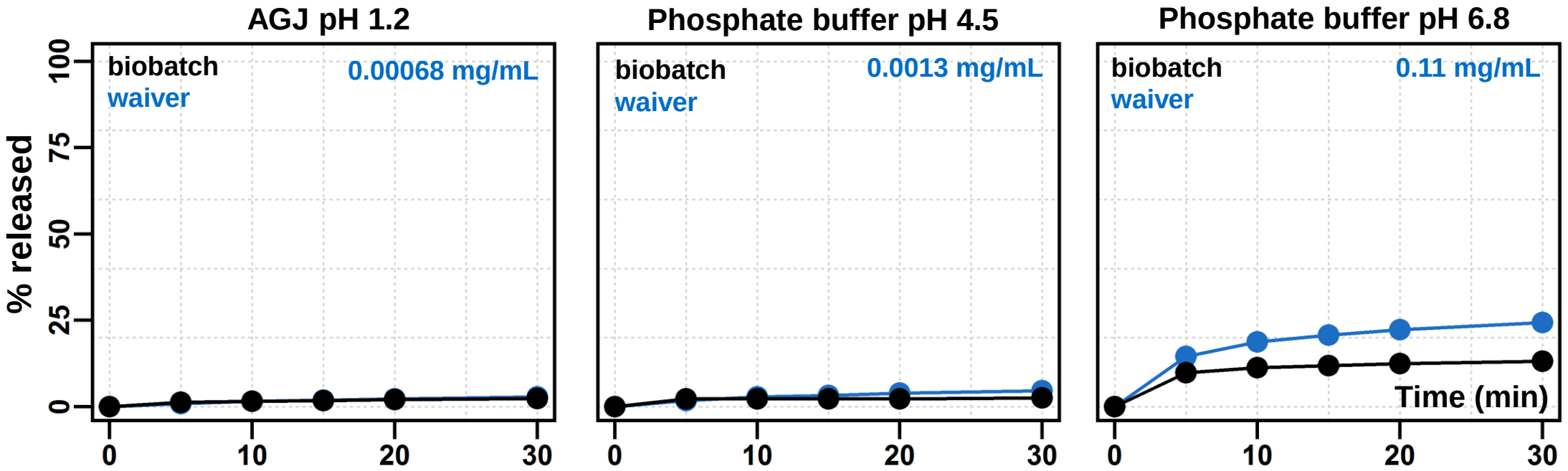


Percentiles (P)			
P	Shah et al.	DDSolver[(1)]	RE (%)
5%	53.01	53.53147	−0.97
95%	68.34	68.72088	−0.55

B=1‘000; [(1)]Zhang et al. (2010)

Shah et al. (1998). Pharm Res 15(6): 889-896;
Zhang et al. (2010). AAPS J. 12(3): 263-267

BOOTSTRAP IN PRACTICE: ROUND 1



Percentiles	
5%	97.9487
50%	98.9720
95%	99.5367

B=50‘000 in DDSolver

Percentiles	
5%	86.9786
50%	89.3210
95%	91.5900

B=50‘000 in DDSolver

Percentiles	
5%	50.6544
50%	52.8409
95%	55.7312

B=50‘000 in DDSolver

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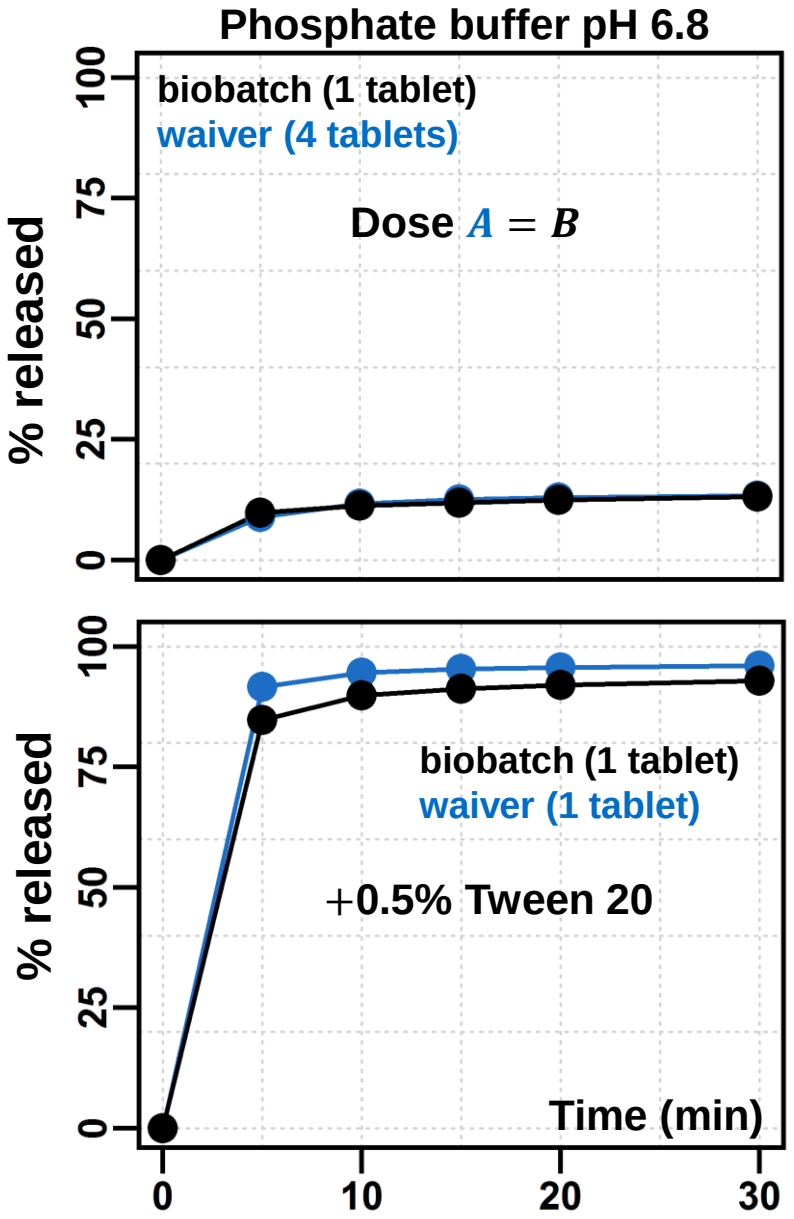
BOOTSTRAP IN PRACTICE: ROUND 2

90% bootstrap CI (Bootf2BCA)[1]		
Type	**Lower**	**Upper**
Percentile	50.6599	55.7327
Bootstrap-*t*[2]	50.7184	56.6114
Normal	50.3144	55.4415
BCa	50.9257	56.3030
Basic	50.1124	55.1852

[1]Mendyk et al., 2013; [2]in-house R-code, R (v3.6.1); B0=50‘000; B1=1‘000

[Response to draft] (…) **to construct more versions of 90% confidence interval (…) to see if results regarding similarity are sufficiently robust.**



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Mendyk et al. (2013). Diss Technol 20(1): 13-17

BOOTSTRAP IN PRACTICE: ROUND 3 & 4

[Response to draft] The assessor still finds unclear what is **difference between normal approximation method and basic** bootstrap (…). The Applicant is asked to fill in this information (…).

Normal approximation

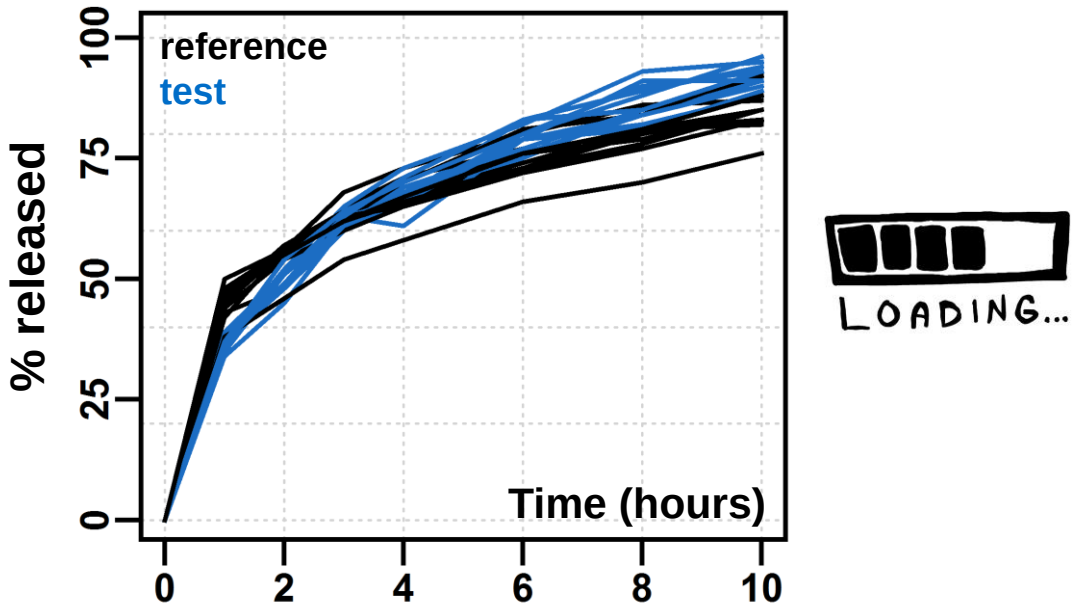
$$\hat{\theta} - b_R \mp v_R{}^{1/2} \cdot z^{(1-\alpha)}$$

Basic (backwards)

$$\left[2\hat{\theta} - \hat{\theta}^{*(1-\alpha)}, 2\hat{\theta} - \hat{\theta}^{*(\alpha)}\right]$$

Davison & Hinkley (1997). Cambridge Press

[Response to final] (…) **the Applicant is asked to provide** (…) **software validation for individual approaches to see that obtained results can be considered as relevant.**



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SUMMARY & QUESTIONS

● **f_2: no control of type I error**	Statistics vs. clinical relevance? Signals of problems available?
● **Bootstrap f_2: confidence interval … but harder to pass similarity criterion**	Type I error control? Which CI? Comparison to other methods? Applicable generally (EMA Q&A)?
● **Equivalence margin: average 10%**	Current margin already conservative? Maximum 10% (EMA Q&A) or average 10%?
● **Dissolution in non-sink conditions**	API or product performance?

QUOTES: LIBRARY(FORTUNES)

```
> library(fortunes)
> fortunes::fortune(222)
```

Some people familiar with R describe it as a supercharged version of Microsoft's Excel spreadsheet software.

-- Ashlee Vance (in his article "Data Analysts Captivated by R's Power") The New York Times (January 2009)

```
> library(fortunes)
> fortunes::fortune(358)
```

The existence of a method is not a sufficient reason to use that method.

-- Jari Oksanen (about relative advantages of several multivariate analysis methods) R-SIG-Ecology (November 2013)

R Core Team (2019). https://www.R-project.org/