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A bayesian framework for conducting effective bridging between references under uncertainty

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Scope

- Vaccines batches potency should be evaluated before being released in the market (in order to ensure their biological efficiency)
- A specific bioassay is used to evaluate the relative potency (RP) of batches. A reference batch is needed.
- Problem:
  - Commercial life of a vaccine = 30 years
  - A reference should be changed every 3-4 years (out of stock or storage)

How to choose the new reference batch ?

- 2 strategies are possible
  - Choose a new reference that is as close as possible to the previous reference
  - Choose randomly a new reference batch
    - compute a corrective factor (=cf) between the 2 references, using a bridging strategy
    - Cf= log(potency ref2)/log(potency ref1)
    - The bioassay is performed using the new reference batch
    - The RP of batches is computed using the new reference
    - Use the corrective factor to obtain the RP of batches as if they were measured using the primary reference (*i.e.* the very first reference).

Question

- How to compute this corrective factor (=cf)?
- Properties of the cf:
  - The cf is estimated with some uncertainty because it relies on limited data (a limited number of experiments are used to compare both references).
- As the number of bridging increases, corrective factors are applied successively to correct the RP, as it was measured against the primary reference. There exists a risk that the corrected RP deviates from the true RP
- Using simulation,
  - Possible to follow the true RP and the RP obtained after correction

Simulation structure

- Simulate fake potency data
  - for batches and references evaluated routinely (→ RP can be computed)
  - for references during a bridging step (→ cf can be computed)
- Obtain RP of batches against the current reference
- Compute corrective factors and correct the RP
- Obtain the true RP (known during simulation)
- Compare the corrected RP with the true RP
- Criteria:
  - Probabilities to accept a batch
  - Bias between the corrected and the true RP

Details for simulation of data (1)

- Inputs: fixed and random intercepts; Residual
- References are batches, intended for special use
  - Same sources of variability and same values

✓ Loop 1 (generate p references)

- True_ref = fixed int + random intercept
- Loop 2 (generate m batches to be compared to true Ref)

  True_batch = fixed int + random intercept

  Observed_batch = N(True_batch, precision) # n times

  Observed_ref = N(True_ref, precision) # n times
- End loop 2

✓ End loop 1

Routine data

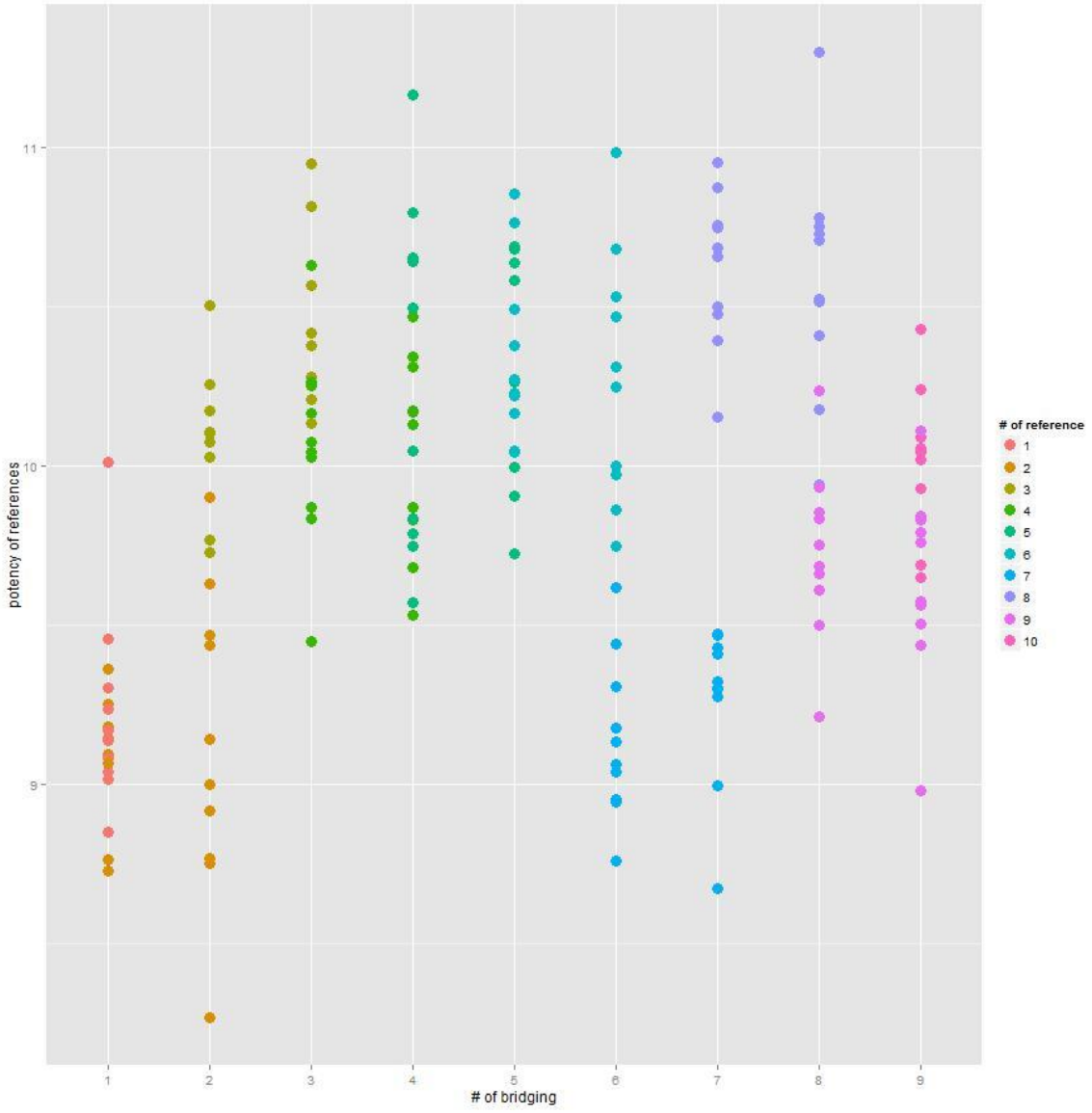
Log-transformed potencies are generated

- Copy paste the true primary reference (to be able to have the true RP)


potencies
11
10
9
0
25
50
75
100
# of measure
obs_batches
obs_references
true_batches
true_references

Details for simulation of data (2)

- In practice, specific data are gathered for the bridging
  - To compare old and new references
- True reference values are known by simulation
- bridging data~N(True_ref,precision)


potency of references
11
10
9
1
2
3
4
5
6
7
8
9
# of bridging
# of reference
1
2
3
4
5
6
7
8
9
10

Simulation endpoints

- True_RP = exp(True_batch – True_primary_ref)
- Corrected_RP = exp(observed_batch – Observed_reference) * cf
- **Bias** = log(Corrected_RP) – log(True_RP)
- **Prob_to_accept_batch** : compare the corrected_RP to a lower and upper specification

Methodologies to compute the cf

- On each bridging step without updates of priors
- On each bridging step with updates of priors
- Global bridging model

By bridging step without updates of the priors

- Observed_ref1 ~ N(mean=μ_{ref1}, variance=var_{ref})
- Observed_ref2 ~ N(mean=μ_{ref2}, variance=var_{ref})
- Priors on
  - μ_{ref1} ~ N(mean=0, var=10000)
  - μ_{ref2} ~ N(mean=0, var=10000)
  - var_{ref} ~ U(0,100000)
- Obtain cf=exp($\mu_{ref2} - \mu_{ref1}$)
- Repeat this for all the bridging and combine the cf to correct the RP as it was measured against the primary reference (and not only against the previous reference)

By bridging with updates of the priors

- Non informative priors on the first bridging
- Extract the posteriors
  - Mean and variance of the second reference → to be used as prior of the same reference for the next bridging
  - Mean and variance of var_{ref} → to be used as prior of var_{ref} for the next bridging (gamma distribution to be informative)

    shape= mean^2/variance and rate=mean/variance (rate = inverse scale)

- Observed_ref1 ~ N(mean=μ_{ref1}, variance=var_{ref})
- Observed_ref2 ~ N(mean=μ_{ref2}, variance=var_{ref})
- Priors (some informative and some non-informative) on
  - μ_{ref1} ~ N(mean=prior_μ_{ref}, var=prior_var_{ref})
  - μ_{ref2} ~ N(mean=0, var=10000)
  - Var_{ref} ~ Gamma(shape=s, rate=r)
- Obtain cf as previously: cf =exp($\mu_{ref2} - \mu_{ref1}$)

Repeat this for all the bridging except the first one

Global bridging model

Ref1	Ref2	Ref3	Ref4	Ref5	Ref6	Ref7	...
First loop; i=[1,2]							
Second loop; i=[1,3]							
3rd loop; i=[1,4]							
4th loop; i=[1,5]							
5th loop; i=[1,6]							
6th loop; i=[1,7]							

- Observed_refi ~ N(mean=μ_{refi}, variance=var_{ref})
- Priors on
  - μ_{refi} ~ N(mean=0, var=10000)
  - var_{ref} ~ U(0,100000)
- Obtain cf=exp($\mu_{refi} - \mu_{ref1}$)
- Repeat this for all the bridging and combine the cf to correct the RP as it was measured against the primary reference (and not only against the previous reference)
- No prior, but all information of previous bridgings is included directly within the likelihood

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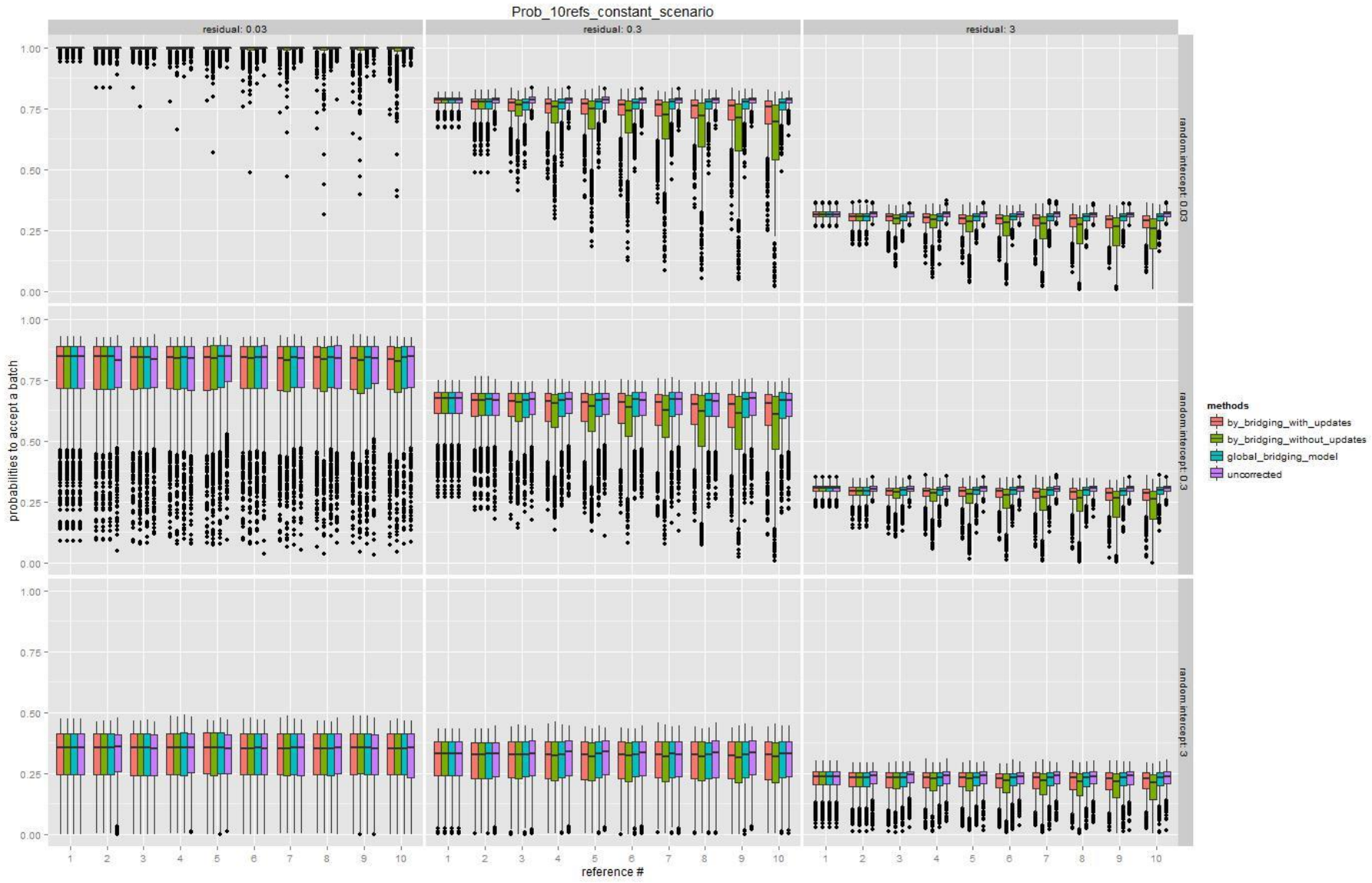
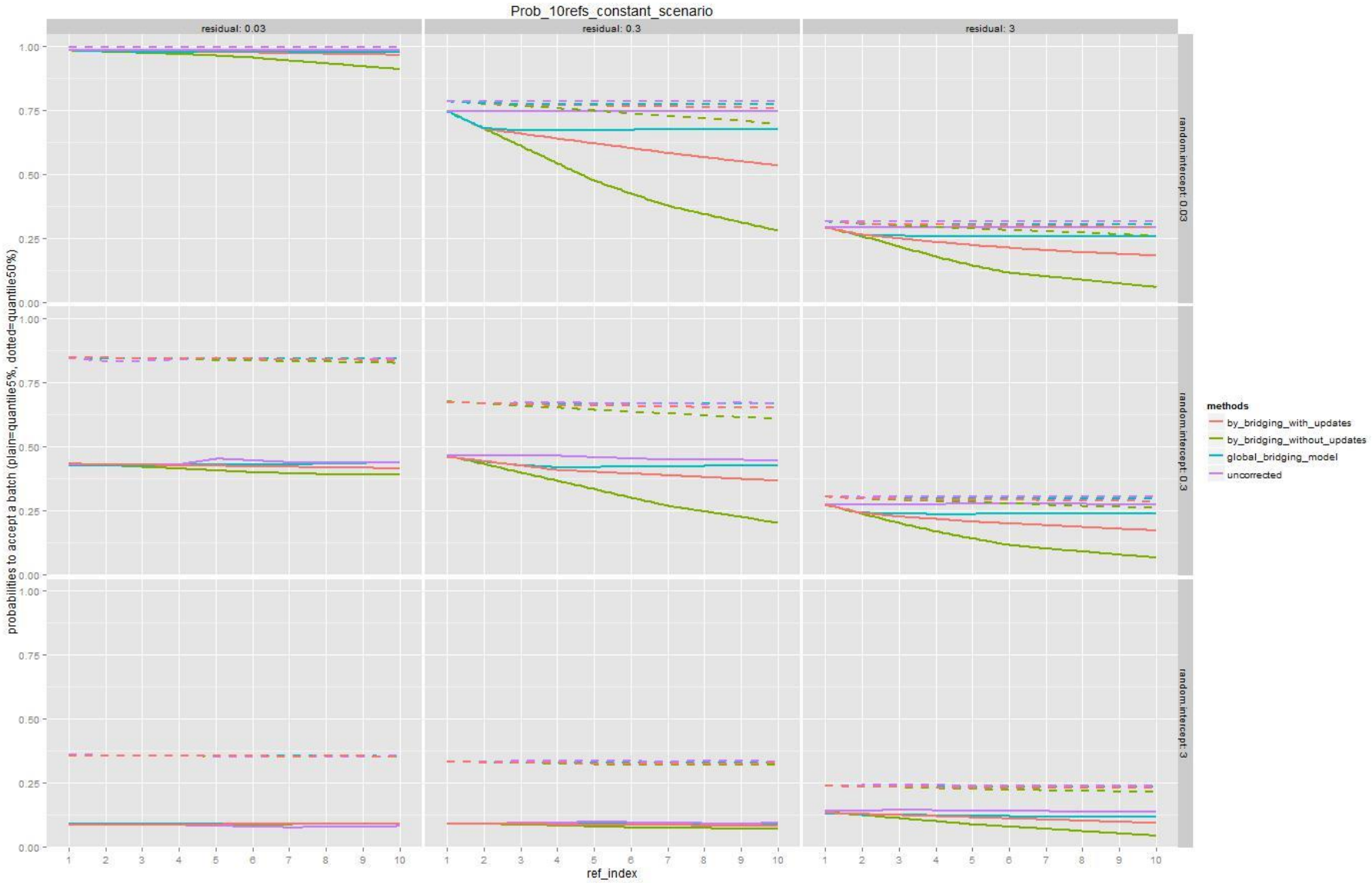
RESULTS

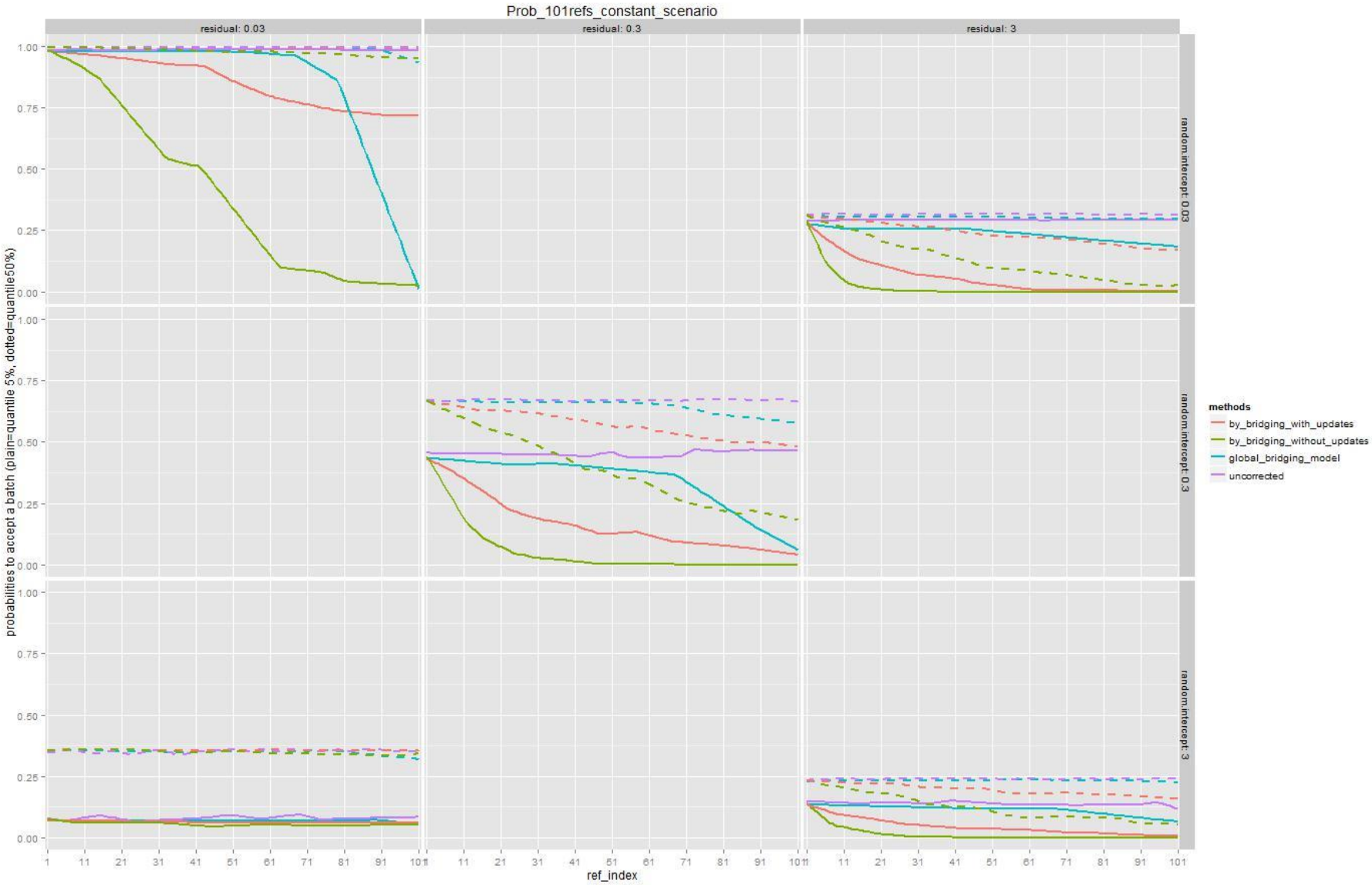
Probabilities in form of box plots



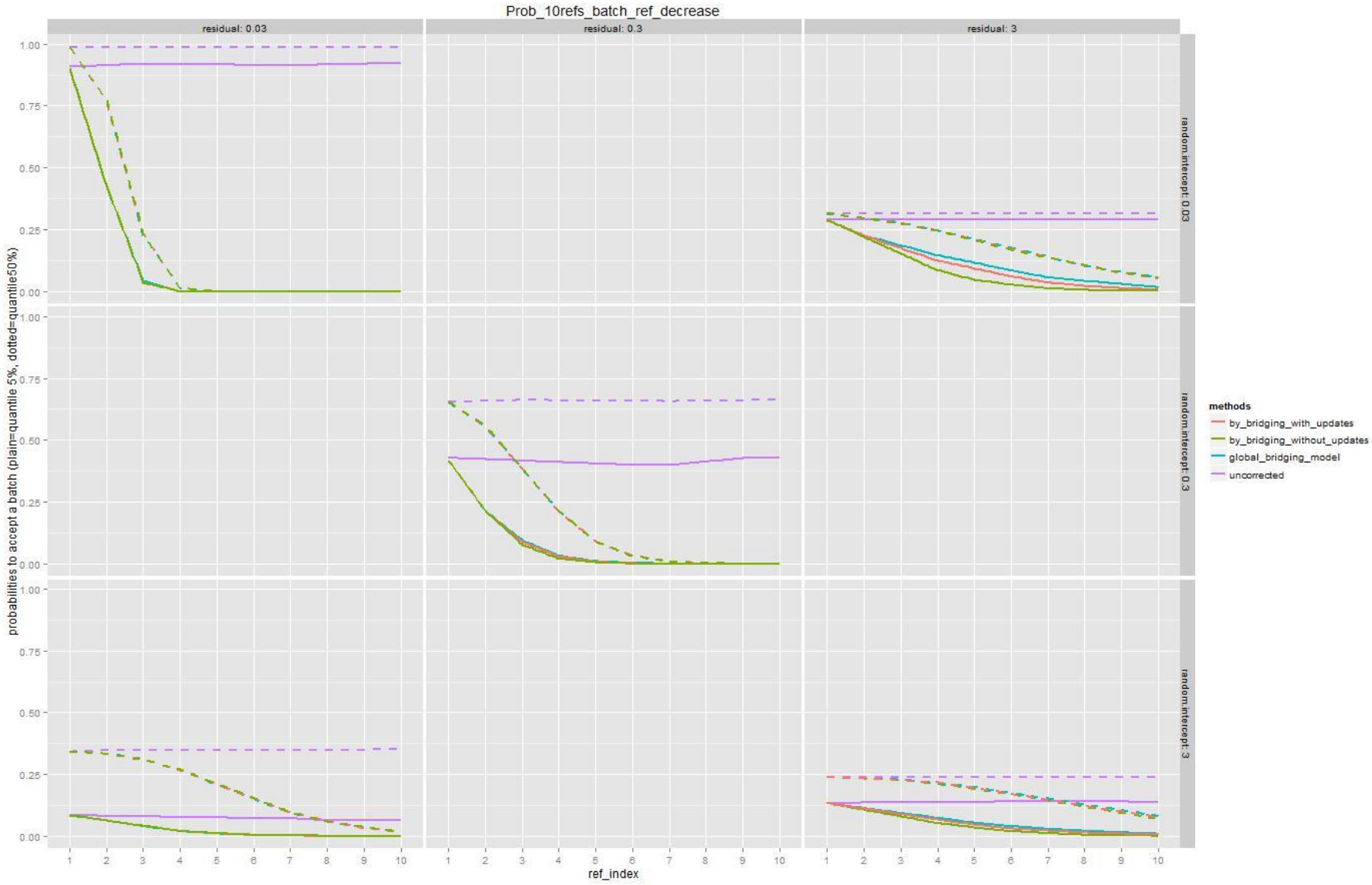
10 refs


Prob_10refs_constant_scenario
residual: 0.03
residual: 0.3
residual: 3
random.intercept: 0.03
random.intercept: 0.3
random.intercept: 3
probabilities to accept a batch (plain=quantile5%, dotted=quantile50%)
1.00
0.75
0.50
0.25
0.00
1 2 3 4 5 6 7 8 9 10
ref_index
methods
by_bridging_with_updates
by_bridging_without_updates
global_bridging_model
uncorrected

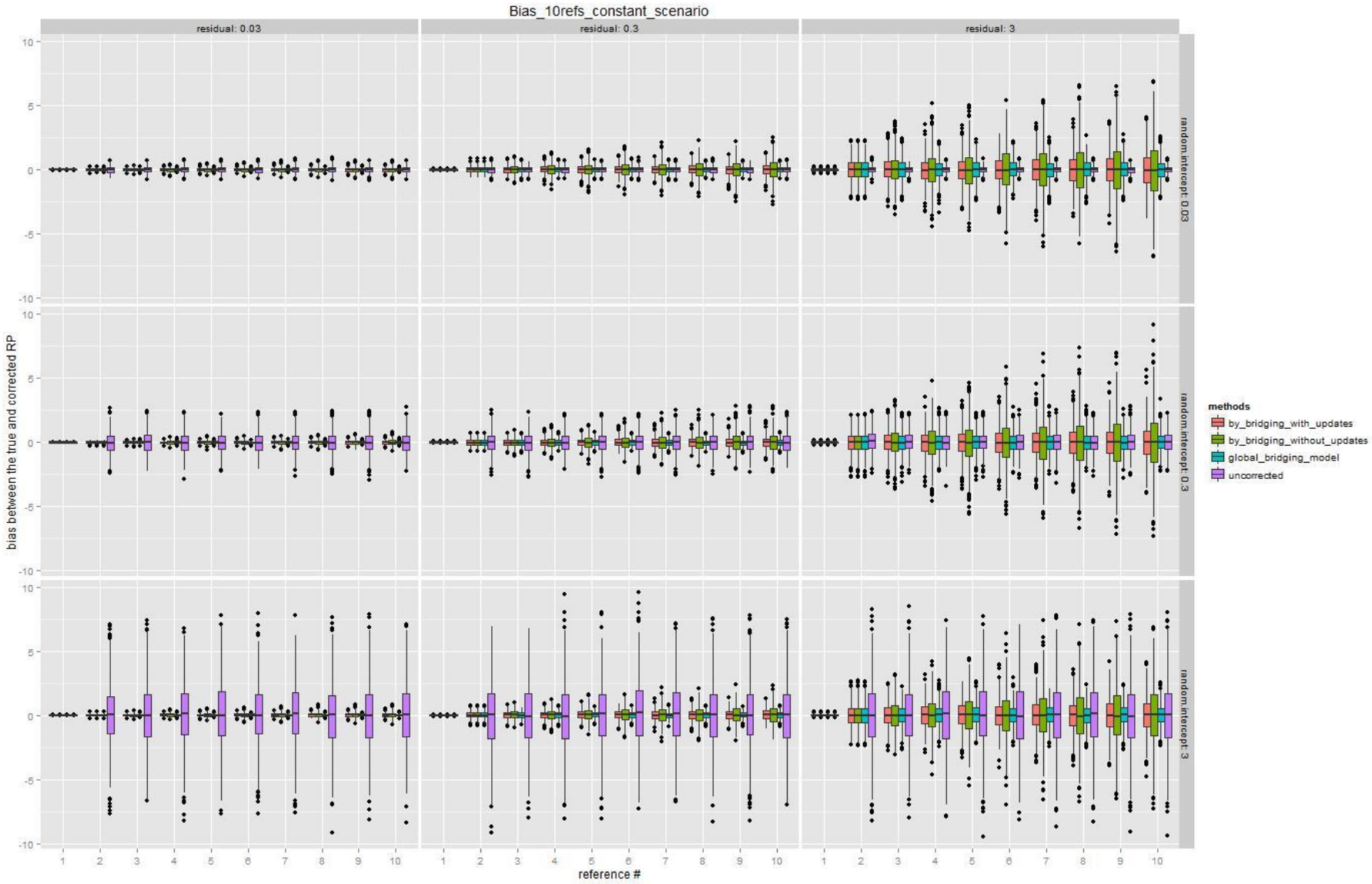
101 refs


Prob_101refs_constant_scenario
residual: 0.03
residual: 0.3
residual: 3
random.intercept: 0.03
random.intercept: 0.3
random.intercept: 3
probabilities to accept a batch (plain=quantile 5%, dotted=quantile50%)
1.00
0.75
0.50
0.25
0.00
1
11
21
31
41
51
61
71
81
91
101
ref_index
methods
by_bridging_with_updates
by_bridging_without_updates
global_bridging_model
uncorrected

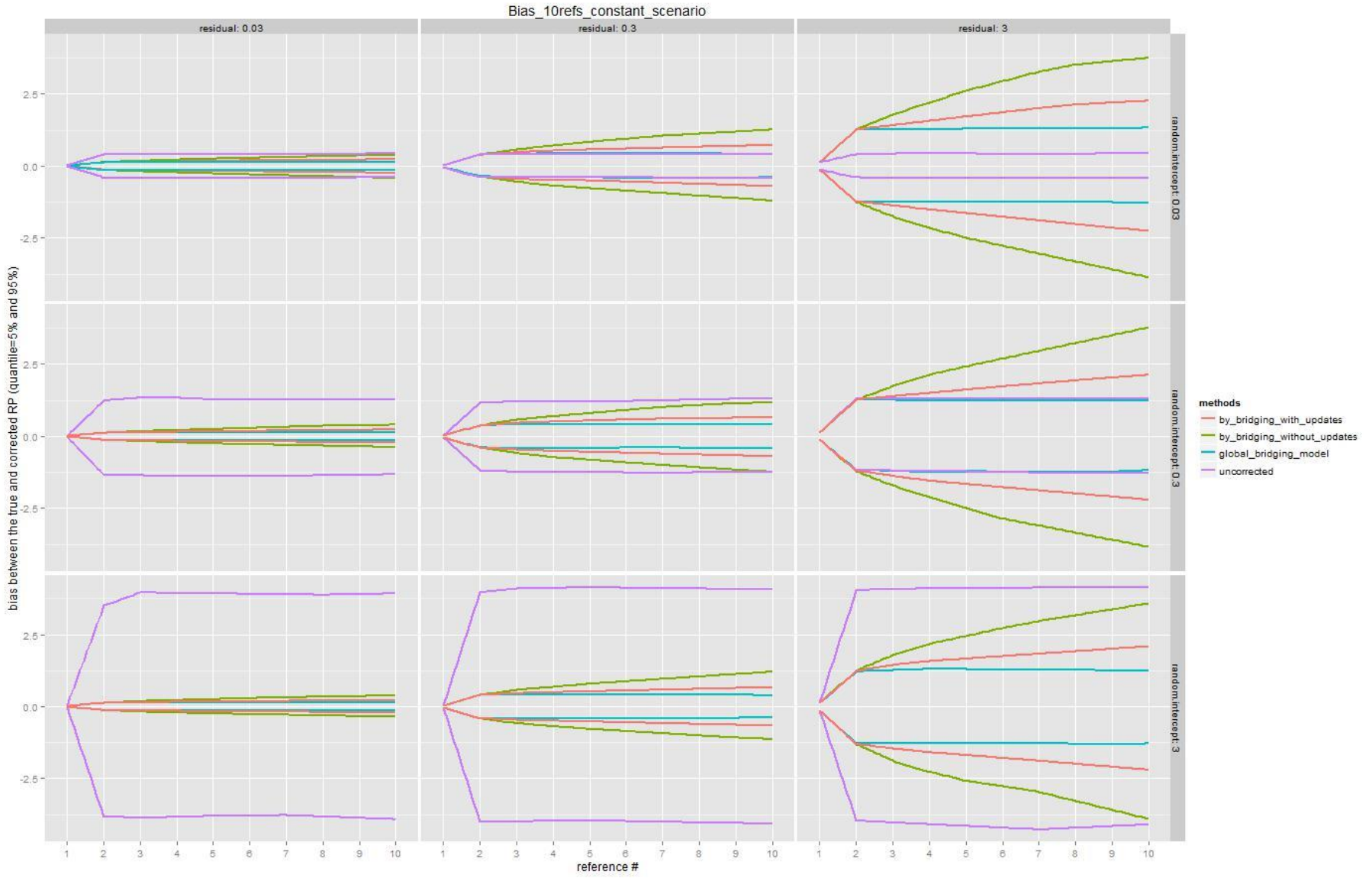
Batches and refs decrease



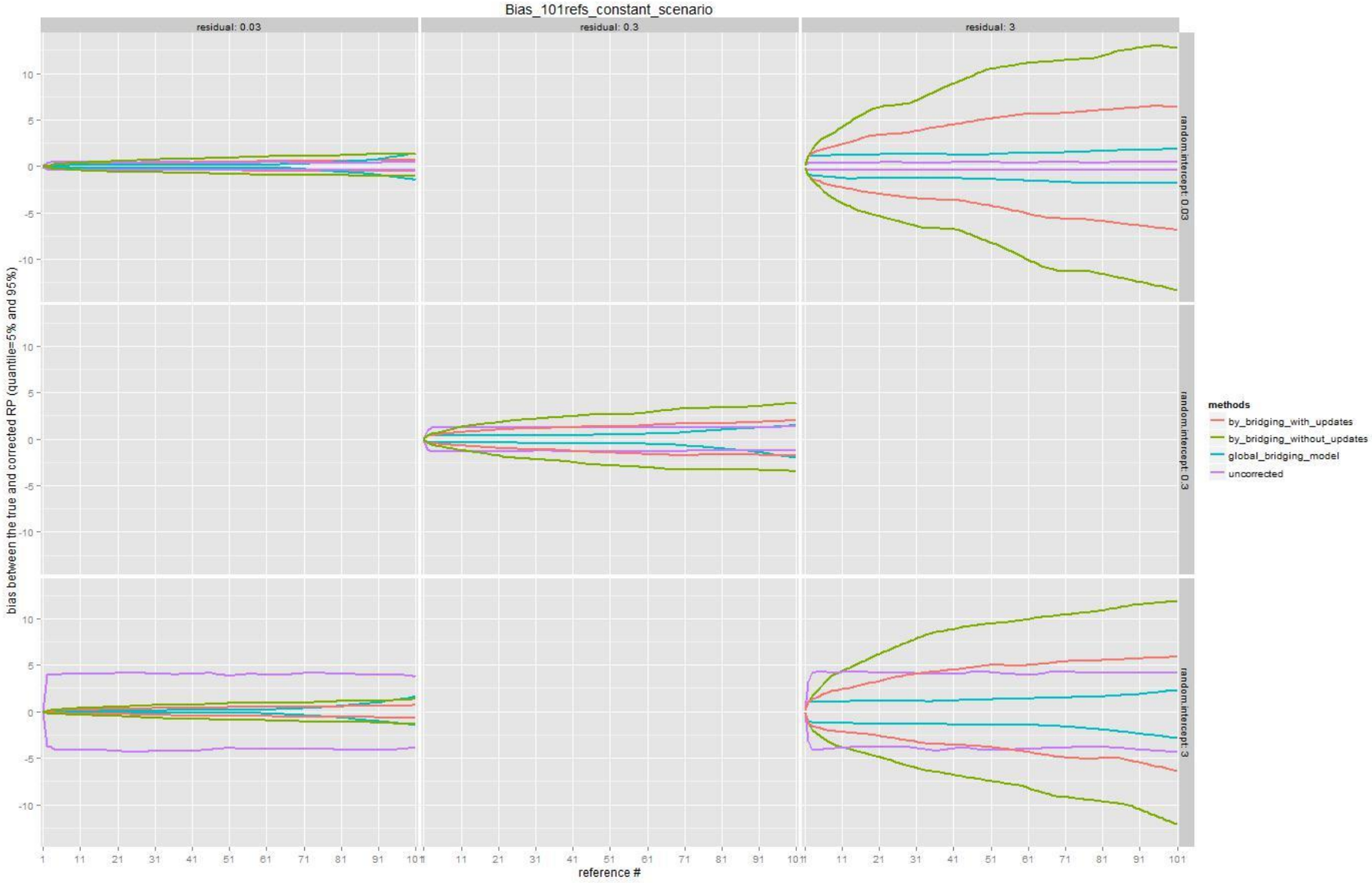
Bias


Bias_10refs_constant_scenario
residual: 0.03
residual: 0.3
residual: 3
random.intercept: 0.03
random.intercept: 0.3
random.intercept: 3
bias between the true and corrected RP
reference #
methods
by_bridging_with_updates
by_bridging_without_updates
global_bridging_model
uncorrected

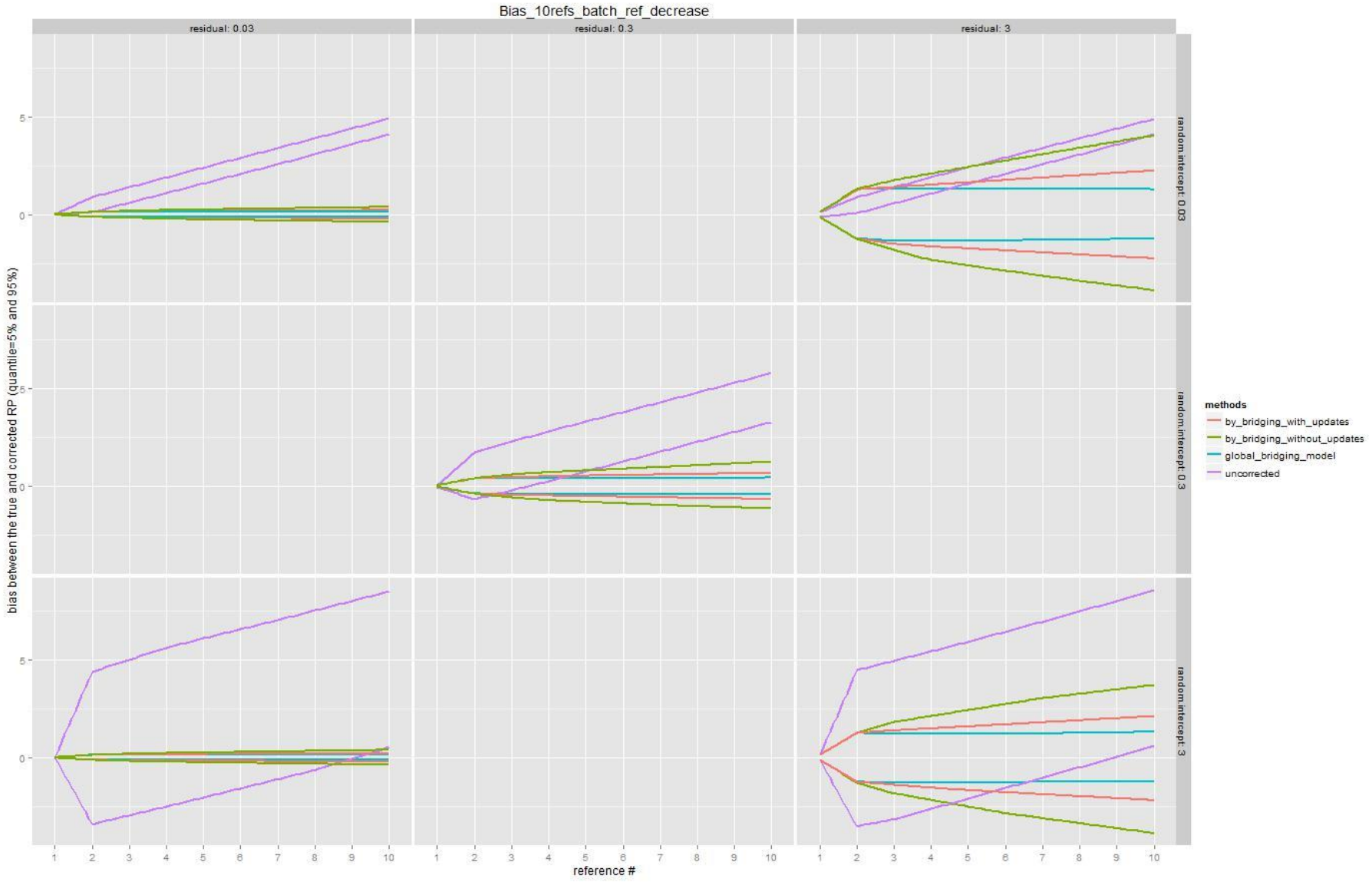
10 refs


Bias_10refs_constant_scenario
residual: 0.03
residual: 0.3
residual: 3
random.intercept: 0.03
random.intercept: 0.3
random.intercept: 3
bias between the true and corrected RP (quantile=5% and 95%)
2.5
0.0
-2.5
1
2
3
4
5
6
7
8
9
10
reference #
methods
by_bridging_with_updates
by_bridging_without_updates
global_bridging_model
uncorrected

101 refs


Bias_101refs_constant_scenario
residual: 0.03
residual: 0.3
residual: 3
random.intercept: 0.03
random.intercept: 0.3
random.intercept: 3
bias between the true and corrected RP (quantile=5% and 95%)
reference #
methods
by_bridging_with_updates
by_bridging_without_updates
global_bridging_model
uncorrected

Batch and refs decreases



Conclusions

- Based on historical data, sources of variability can be derived and simulation based on historical data can be performed
- When sources of variability are large, it can be unnecessary to correct the RP
- 2 methods with informative priors
  - Formally updating the priors at each step
  - The priors are contained in the data and the data are injected in the model
- Such models can include in the priors information on the stability of the reference

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Additionnal slides

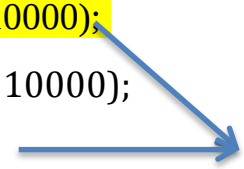
By bridging without update of priors

```
proc mcmc data=&bridging_. nmc=25000 thin=5 nbi=2500 seed=0
                           mchistory=detailed monitor=(cf);
                           array logmuref[2] logmuref1 logmuref2;
                           parms logmuref1 5 ;
                           parms logmuref2 5 ;
                           parms precref 5;
                           prior logmuref1~ normal(mean = 0, var = 10000);
                           prior logmuref2~ normal(mean = 0, var = 10000);
                           prior precref ~ uniform(0,100000);
                           cf = 2**(logmuref2- logmuref1);
                           model data ~ normal(logmuref[refid], prec = precref);
run;
quit;
```

By bridging with update of priors

first bridging is the same as before

```
proc mcmc data=&bridging_. nmc=25000 thin=5 nbi=2500 seed=0
                    mchistory=detailed monitor=(cf);
                    array logmuref[2] logmuref1 logmuref2;
                    parms logmuref1 5 ;
                    parms logmuref2 5 ;
                    parms precref 5;
                    prior logmuref1~ normal(mean = 0, var = 10000);
                    prior logmuref2~ normal(mean = 0, var = 10000);
                    prior precref ~ uniform(0,100000);
                    cf = 2**(logmuref2- logmuref1);
                    model data ~ normal(logmuref[refid], prec = precref);
run;
quit;
```



To be updated

By bridging with update of priors

```
proc mcmc data=&bridging_._&i. nmc=25000 thin=5 nbi=2500 seed=0
                                mchistory=detailed monitor=(cf precref logmuref2);
                                by replicate_simulation;
                                array logmuref[2] logmuref1 logmuref2;
                                parms logmuref1 5 ;
                                parms logmuref2 5 ;
                                parms precref 5;
                                prior logmuref1~ normal(mean = mean_logmuref, var = variance_logmuref);
                                prior logmuref2~ normal(mean = 0, var = 10000);
                                prior precref  ~ gamma(s, iscale=r) ;
                                cf = 2**(logmuref2- logmuref1);
                                model data ~ normal(logmuref[refid], prec = precref);
                                ods output postSummaries=mcmc_postsummaries_&i.;
run;
quit;
```

Global model

```
proc mcmc data=&bridging_. nmc=25000 thin=5 nbi=2500 seed=0
                    mchistory=detailed monitor=(cf);
                    array logmuref[&j.] ;
                    parms logmuref: 5 ;
                    parms precref 5;
                    prior logmuref: ~ normal(mean = 0, var = 10000);
                    prior precref ~ uniform(0,100000);
                    cf = 2**(logmuref[&j.]- logmuref1);
                    model data ~ normal(logmuref[ref_nbr], prec = precref);
                    where bridging_nbr <= &i.;
                    ods output postSummaries=postSummaries_&i.;
                    ods output postIntervals=postIntervals_&i.;

run;
quit;
```