

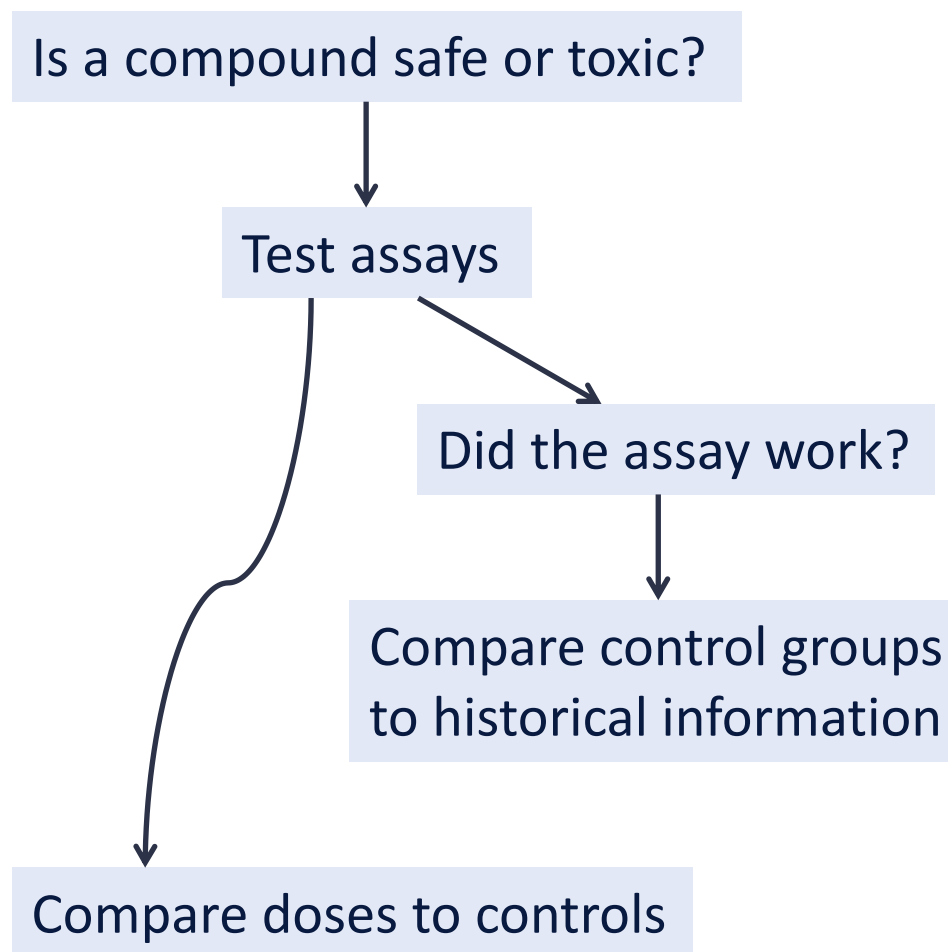
Non-Clinical Statistics Conference, Padua, 2026

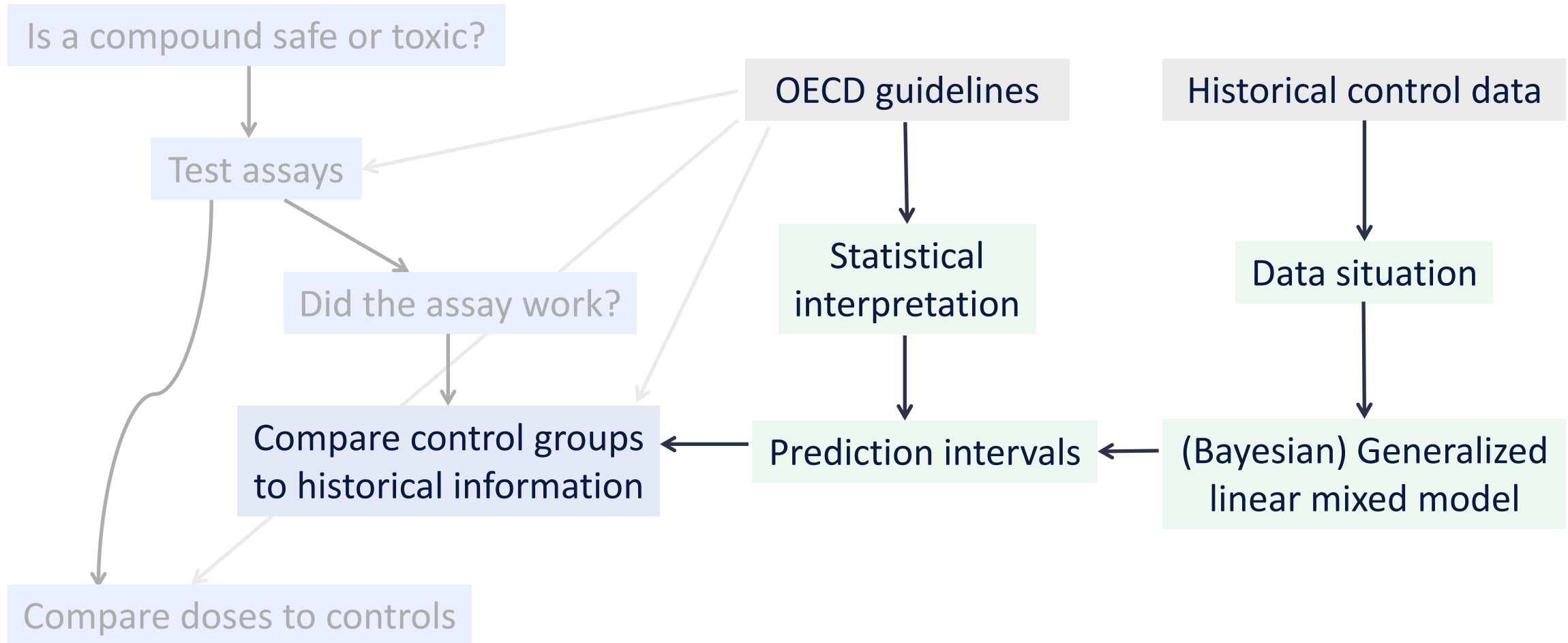
Bayesian prediction intervals for genetic toxicology assays using historical control data

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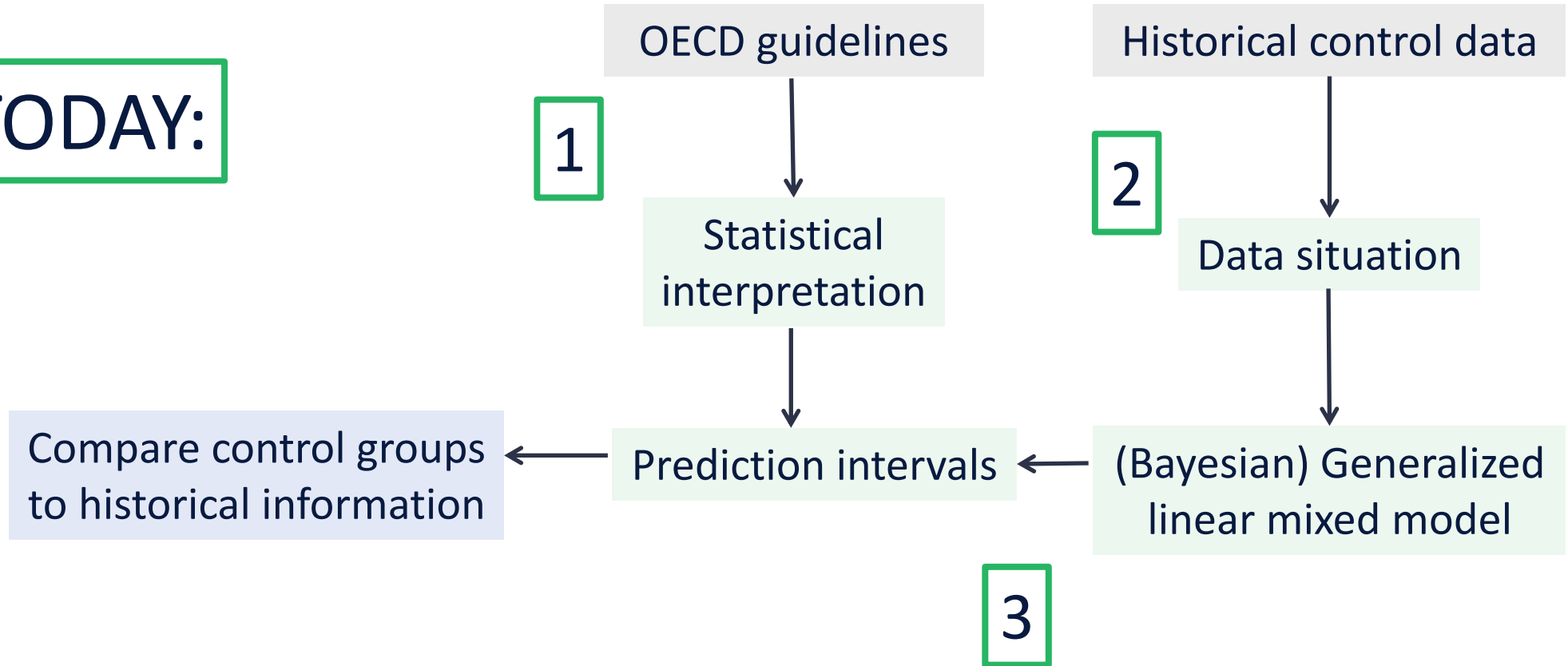
Disclaimer

All points presented here reflect the authors' personal views and do not necessarily correspond to positions of the organizations to which they belong.





TODAY:



Statistical details in guidelines

“Statistical methods may be used as an aid in evaluating the test results.”
- Guideline on Ames test (1997/2020)

- Lists of criteria for assay acceptability and genotoxicity
- Requiring “historical control limits” / “historical distribution”
- Some examples for these concepts
 - Guidelines on micronucleus tests in-vitro and in-vivo (2016)

2025: new guideline on transgenic rodent mutation test

- More precise statistical/mathematical details
- **Prediction intervals** and **tolerance intervals** as “appropriate methods”

Using historical control information

Assay acceptability:

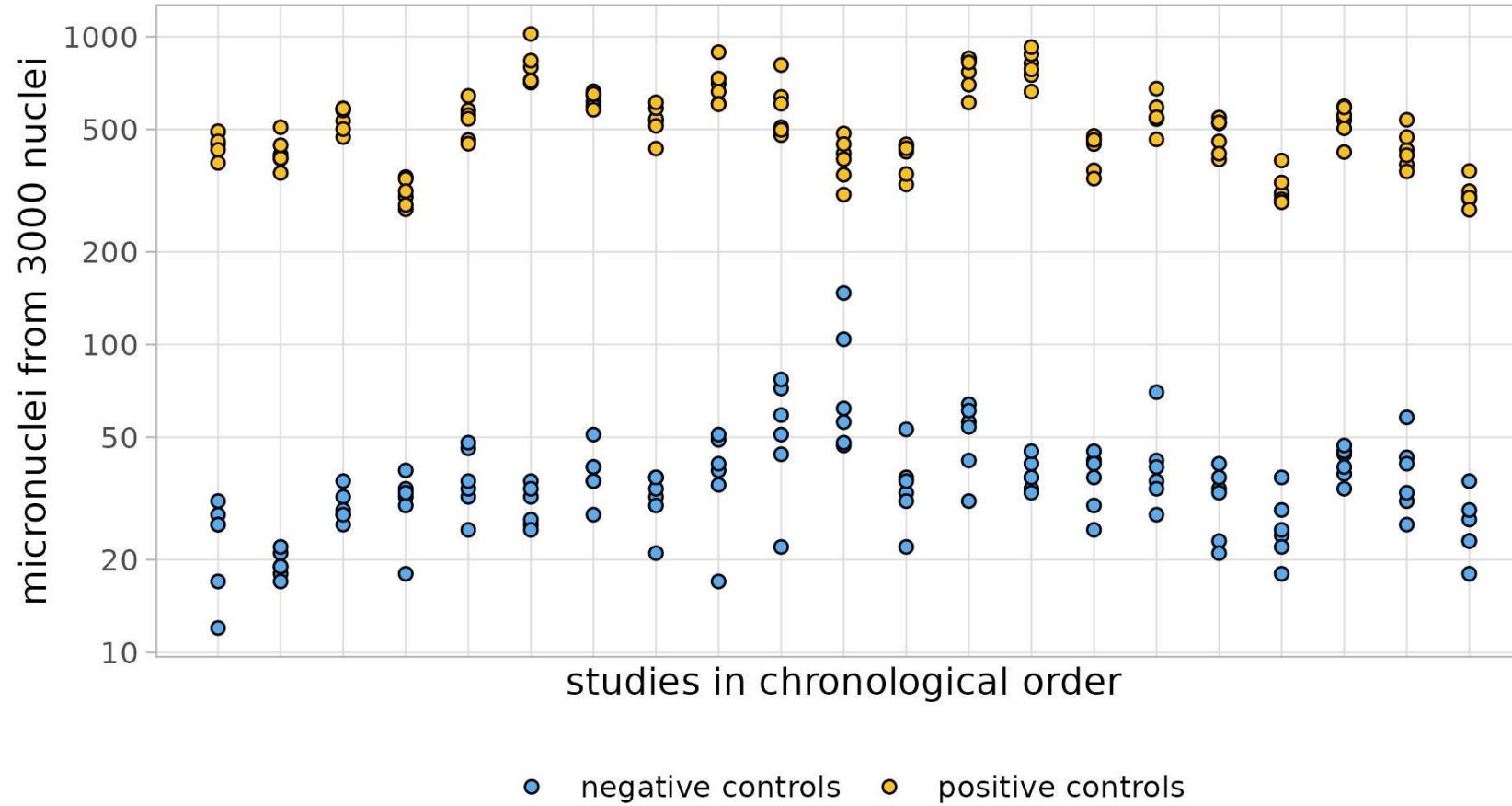
-  • Current vs. historical negative controls
-  • Current vs. historical positive controls
-  • Positive control response (ratio to negative) compared to historical data

Genotoxicity assessment:

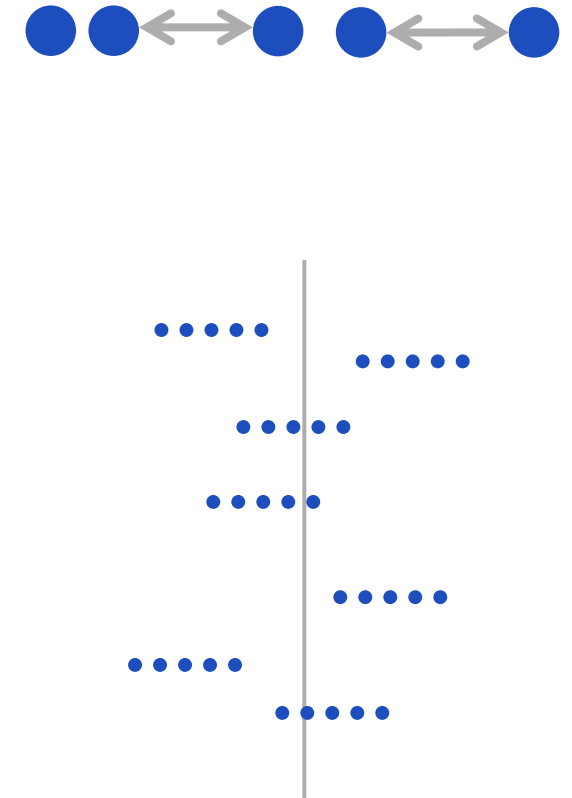
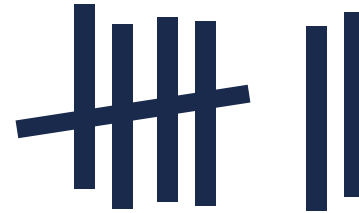
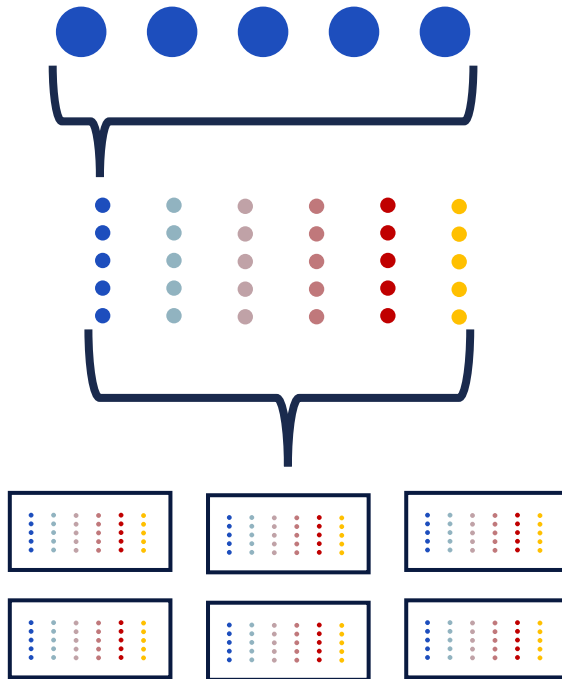
- a) Test-substance vs. current negative control
- b) Dose-response trend
-  c) Test-substance compared to historical negative controls

Data situations

MNT-in-vitro example data



Data situations



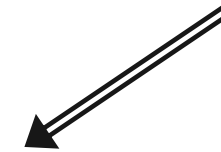
Needs in practice / model requirements

- “Historical distribution”
- “Range”, “Control limits”
- ! • To compare with data (not parameters) !



- Prediction
- Simultaneously for several correlated units and their aggregation

- Count data
- Hierarchical structure
- Overdispersion
- Random experiment effects

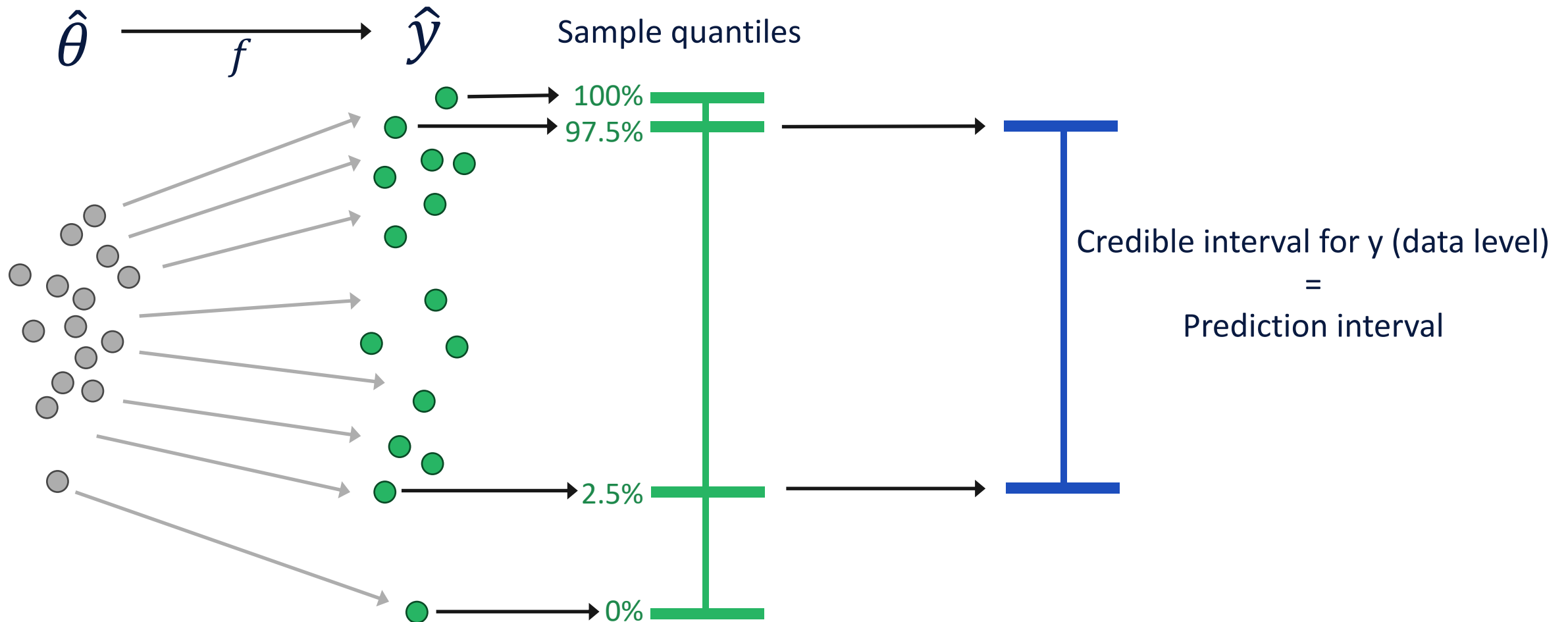


Generalized linear mixed model



- Bayesian GLMM
- Posterior predictive distribution

Bayesian prediction interval

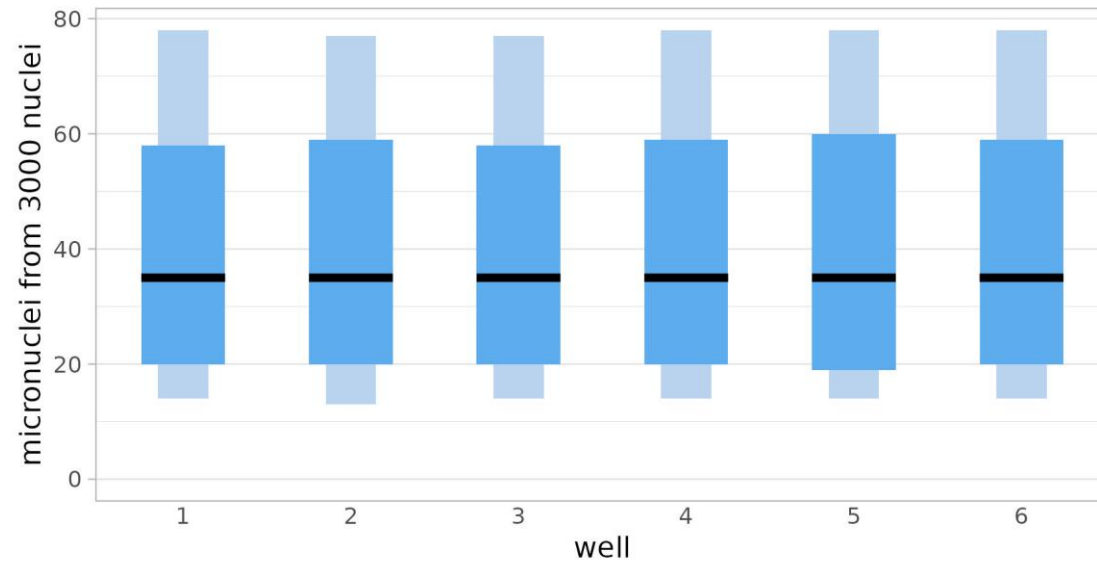


Example modelling

```
brms::brm(  
  formula = brms::bf(  
    micronuclei ~ 0 + offset(log(nuclei)) + group + (0 + group | study),  
    shape ~ 0 + group  
  ),  
  family = brms::negbinomial()  
) |>  
brms::posterior_predict(  
  newdata = data.frame(  
    study = rep(0, times = 2*6),  
    group = rep(c('negative', 'positive'), each = 6),  
    well = -(1:(2*6)),  
    nuclei = rep(3000, times = 2*6)  
  ),  
  allow_new_levels = TRUE,  
  sample_new_levels = 'gaussian'  
)
```

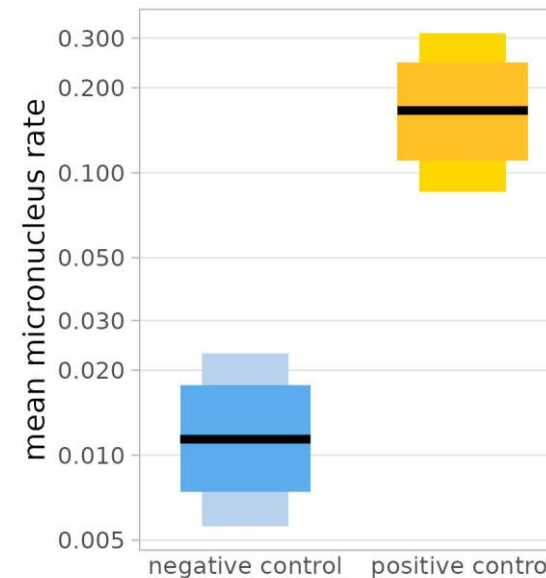
Practical results / advantages

Point-wise posterior predictive for negative control group
quantiles 2.5%, 10%, 50%, 90%, 97.5%

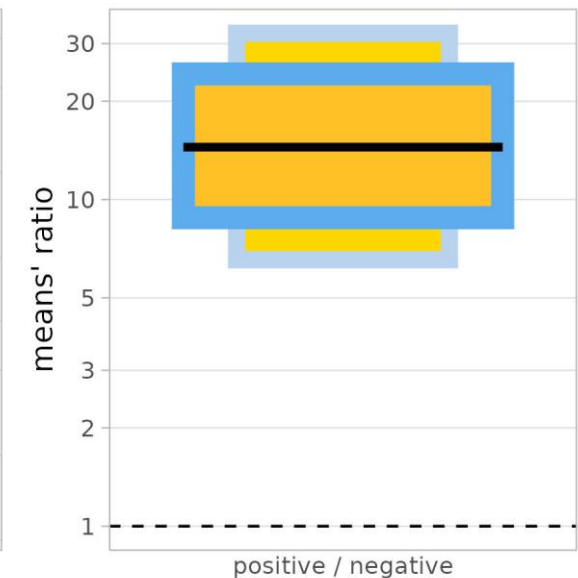


Prediction-intervals for individual values,
group means and their ratio

Groups' means
posterior predictive



Means' ratio
posterior predictive

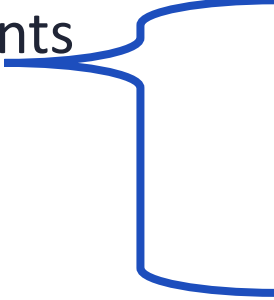


Practical results / advantages

- Intervals taken for “control limits”
- More reliable than range (min and max) or mean $\pm$ SD to answer:
 - “Is this observation plausible?”
 - “Is the experiment under control?”
 - “How does a dose-group appear in light of historical data?”
- Short characterization of “historical distribution”
- Inclusion in routine study reports

Practical results / advantages

Easily adaptable:

- Other assays and endpoints
 - Using other distribution families and models
 - Covariates like sex
- 
- ✓ Micronucleus test in-vitro
 - ✓ Micronucleus test in-vivo
 - Ames test

Current topics

Use regarding “c-criterion” (test substances in light of historical distribution):

- Simultaneous prediction across groups
- Unclear correlations between other groups
- Incorporation of historical dose group data?

Take home

- Historical control information needed at several steps in assay evaluation
- Adaptable evaluation strategies across genetic toxicology assays
- Prediction intervals for comparisons on observation level



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