Basic Science of Measurement: Metrology Principles for Biomarkers

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Metrology

- Systematic principles yield measurement results I can be confident in…
  - Traceability
  - Measurement Uncertainty
  - Method Validation

Traceability

- tying results to a common reference
  - usually realized with calibration
  - enables comparison of results amongst those using the common reference
    - across space and time
  - think meter, kilogram, second…
- biomarkers are often traceable to a *control group*
  - enrichment of a molecular signal

Measurement Uncertainty

- estimated value that gives me reasonable expectation of dispersion around my result
  - given my measurement system
  - combination of all sources of variability or limitations in knowledge through the process

Method Validation

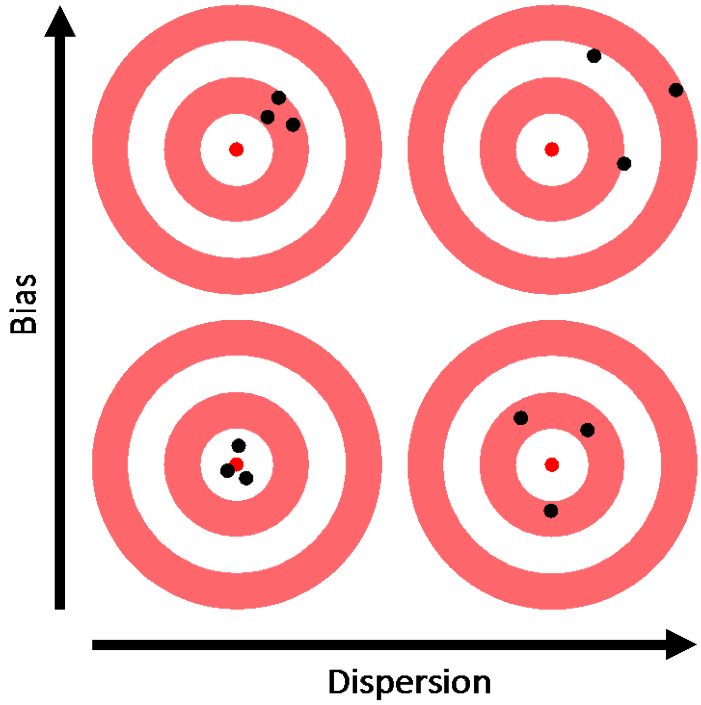
- Demonstration by provision of objective evidence…
  - that what I'm measuring is what I intend to be measuring
  - prove I'm not just reporting artifacts
- *Analytical Validation, which is* Distinct from *Clinical Validation*

Confidence

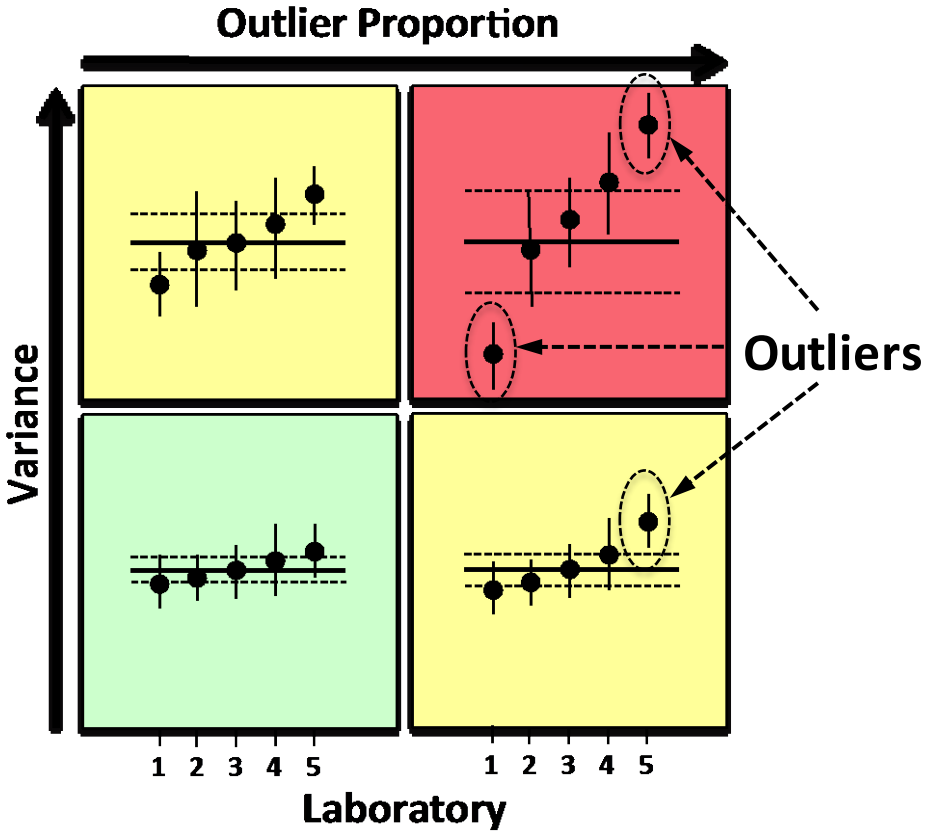
- Sort these bits out, and I can be confident that my measurement results are…
  - not artifact
  - comparable to other results
  - will take on a range of likely values, with a known likelihood
- Now, I can make decisions.

We can evaluate results with interlab studies

Accuracy and Precision

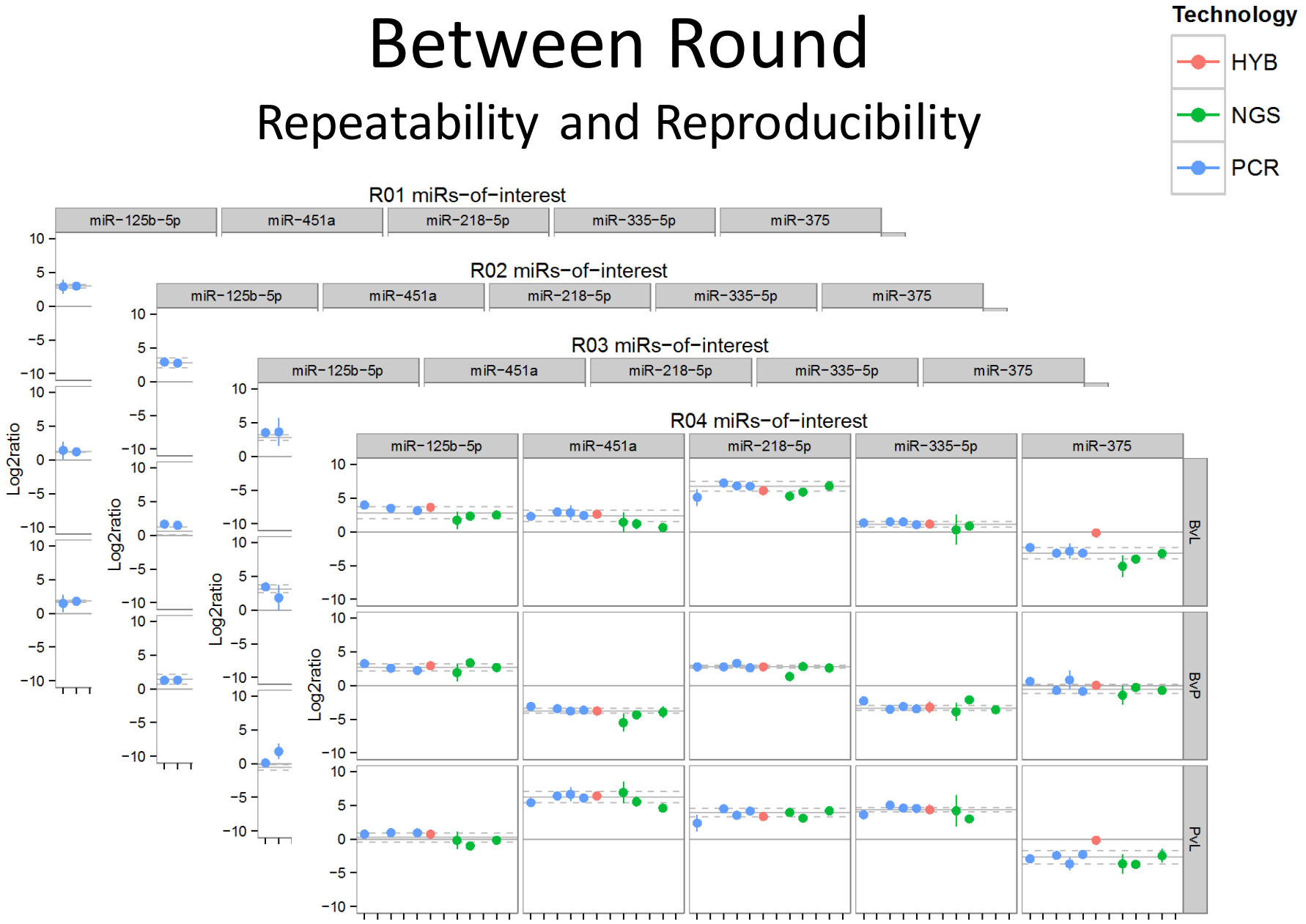


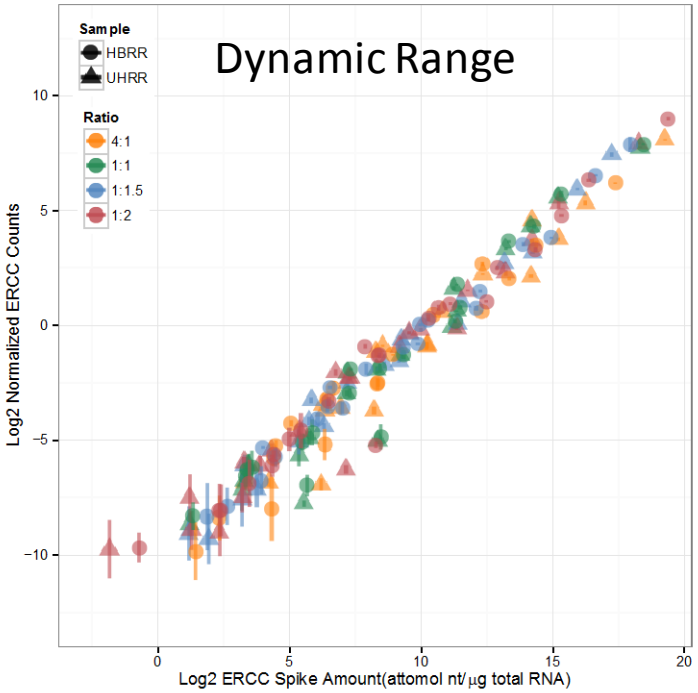
Repeatability and Reproducibility

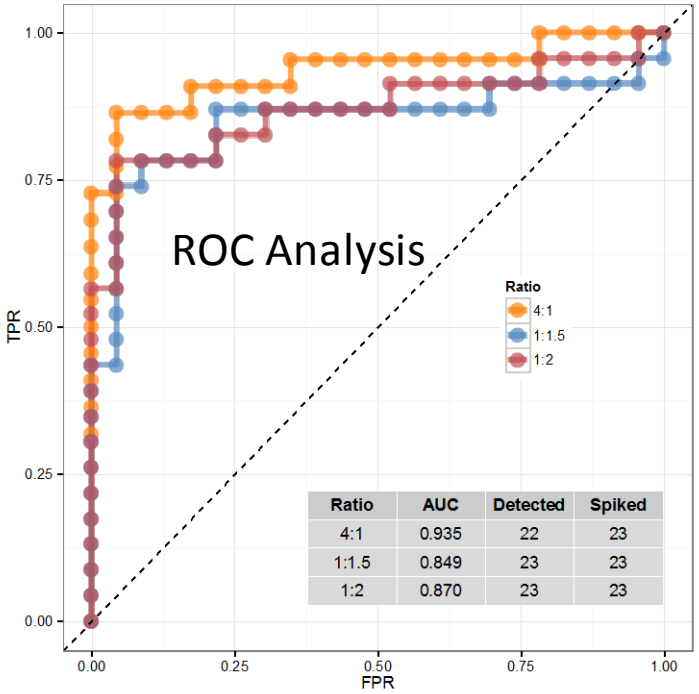


Between Round

Repeatability and Reproducibility

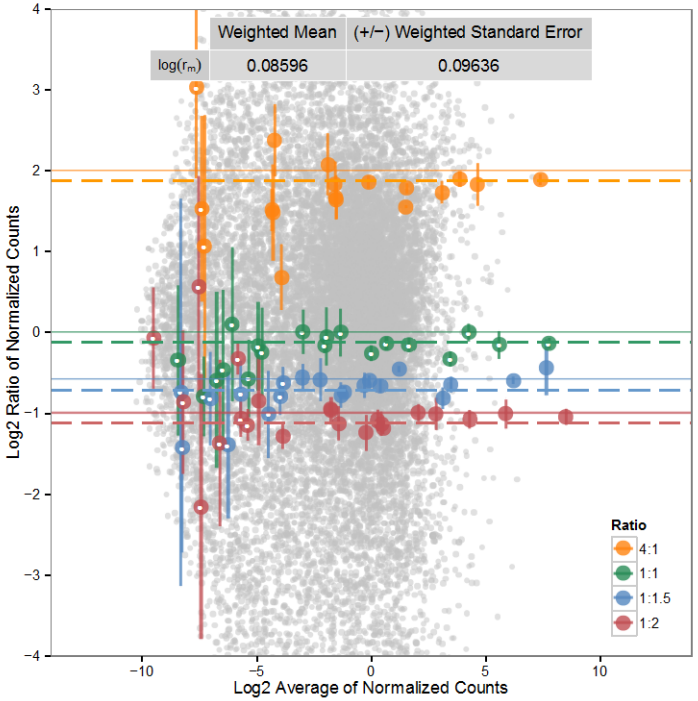


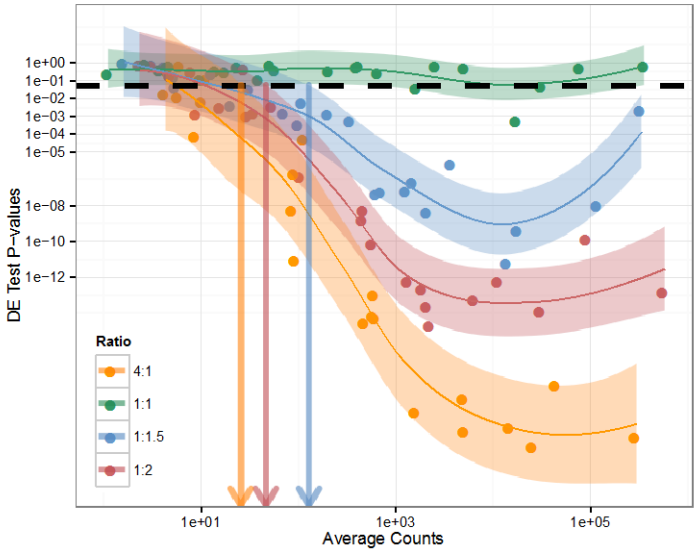




Ratio	AUC	Detected	Spiked
4:1	0.935	22	23
1:1.5	0.849	23	23
1:2	0.870	23	23

MA Plot

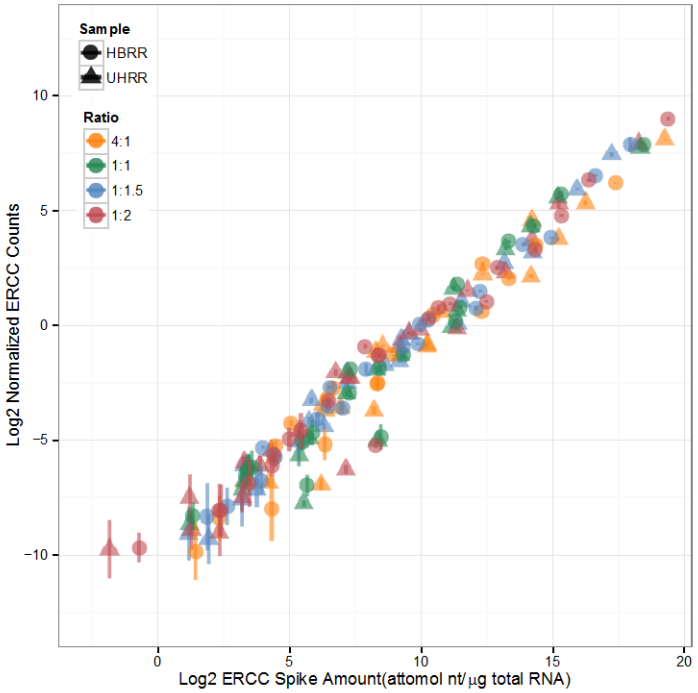


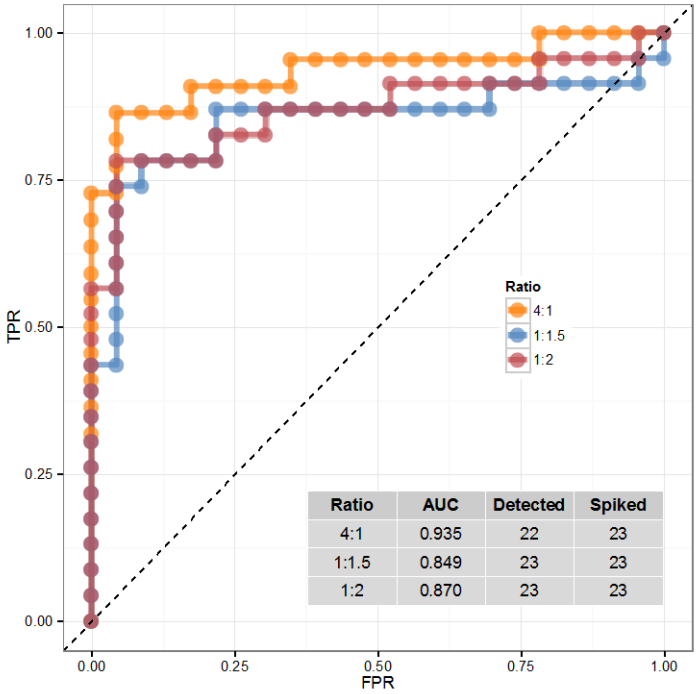


Ratio LOD

Ratio	LODR Estimate	90% CI Lower Bound	90% CI Upper Bound
4:1	26	9.8	40
1:1.5	130	43	160
1:2	47	26	61

Good Lab





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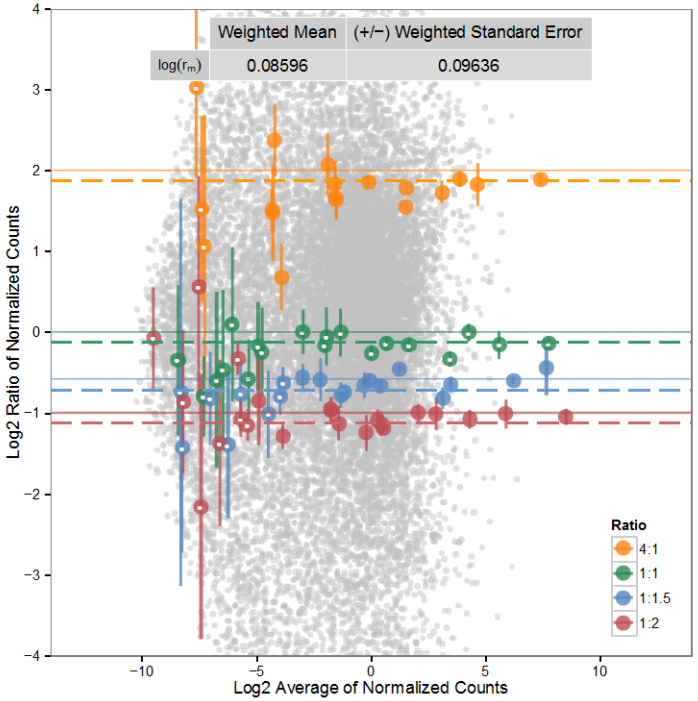
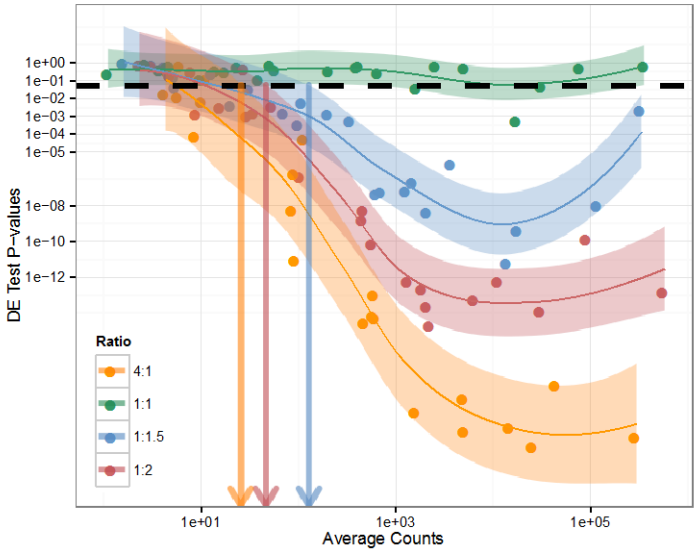
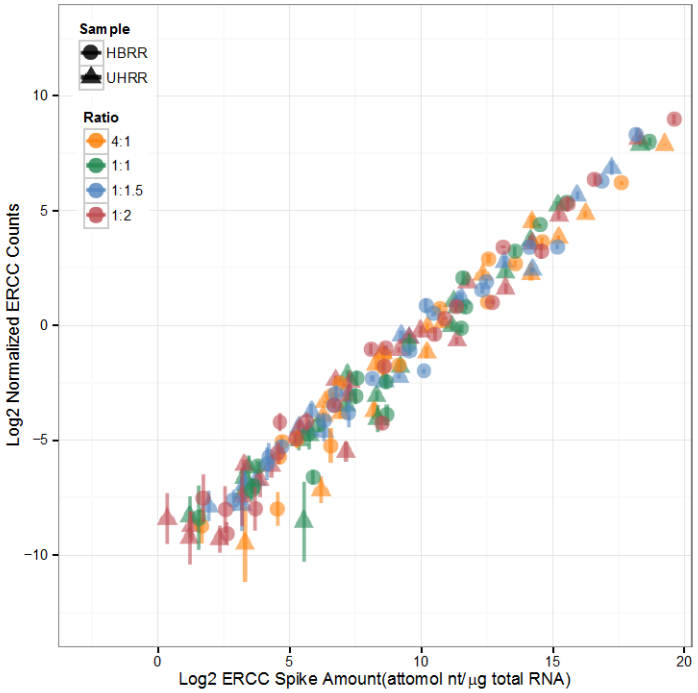
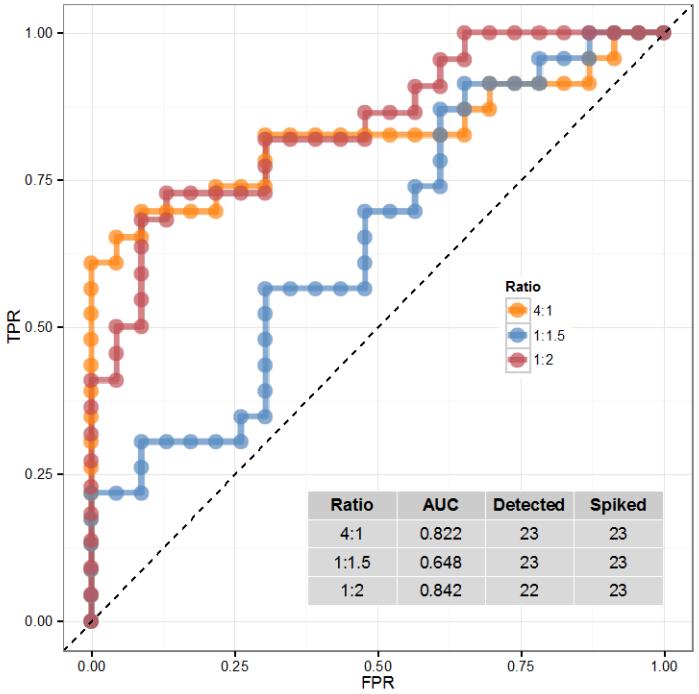




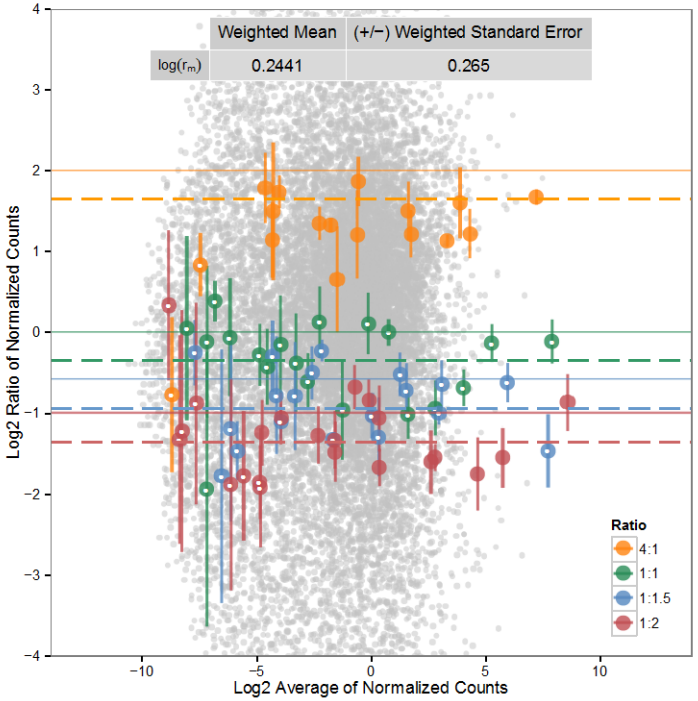
Ratio	LODR Estimate	90% CI Lower Bound	90% CI Upper Bound
4:1	26	9.8	40
1:1.5	130	43	160
1:2	47	26	61

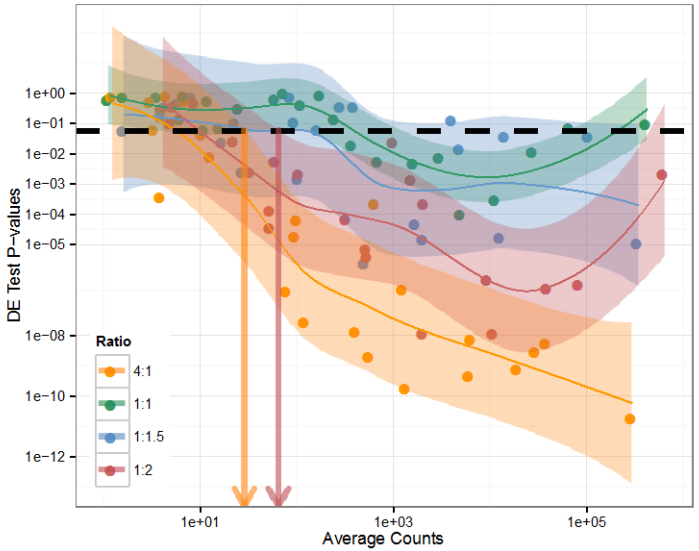
Bad Lab





Ratio	AUC	Detected	Spiked
4:1	0.822	23	23
1:1.5	0.648	23	23
1:2	0.842	22	23





Ratio	LODR Estimate	90% CI Lower Bound	90% CI Upper Bound
4:1	29	12	39
1:1.5	Inf	NA	NA
1:2	65	20	230

Metrology

- Systematic principles yield measurement results I can be confident in…
  - Traceability
  - Measurement Uncertainty
  - Method Validation