Introduction to ChIP-seq peak calling and differential peak calling

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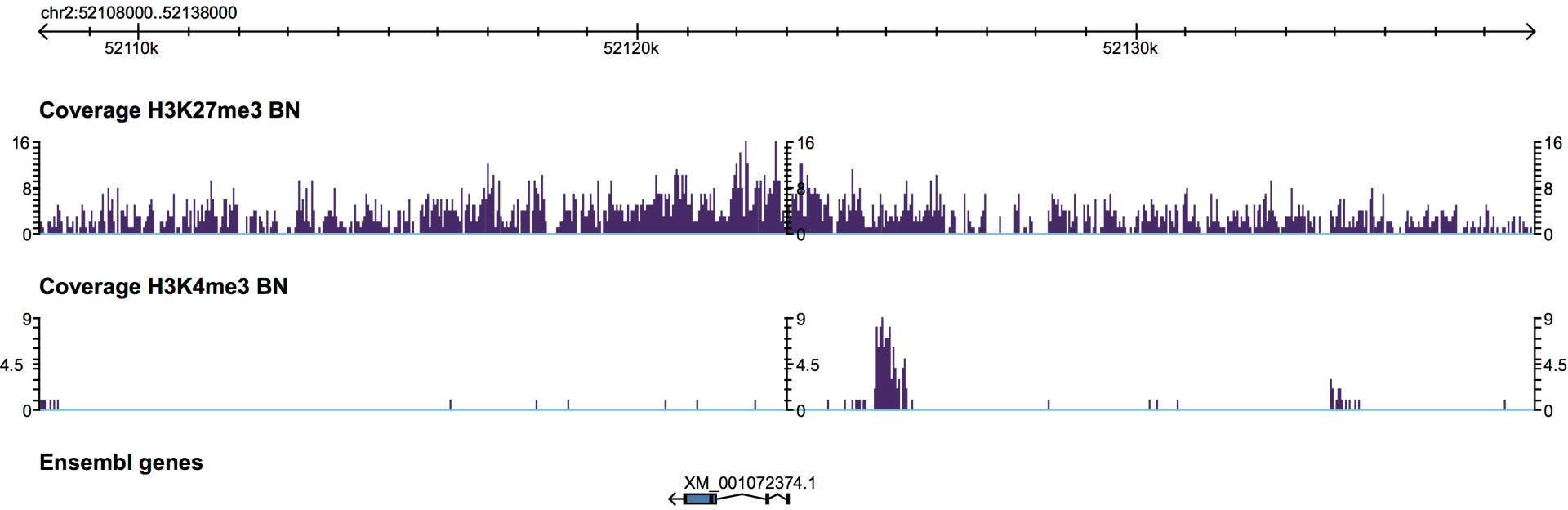
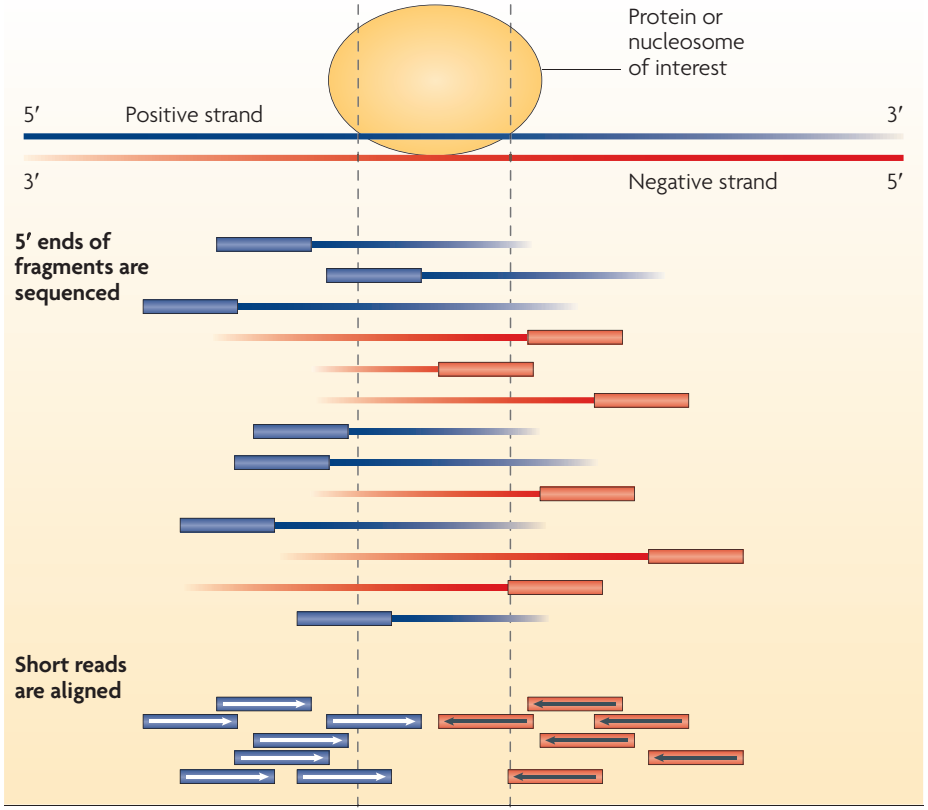
ChIP-seq tracks



- Signal to noise ratio
  - High for peak like features
  - Low(er) for large domain features

Coverage / read counts

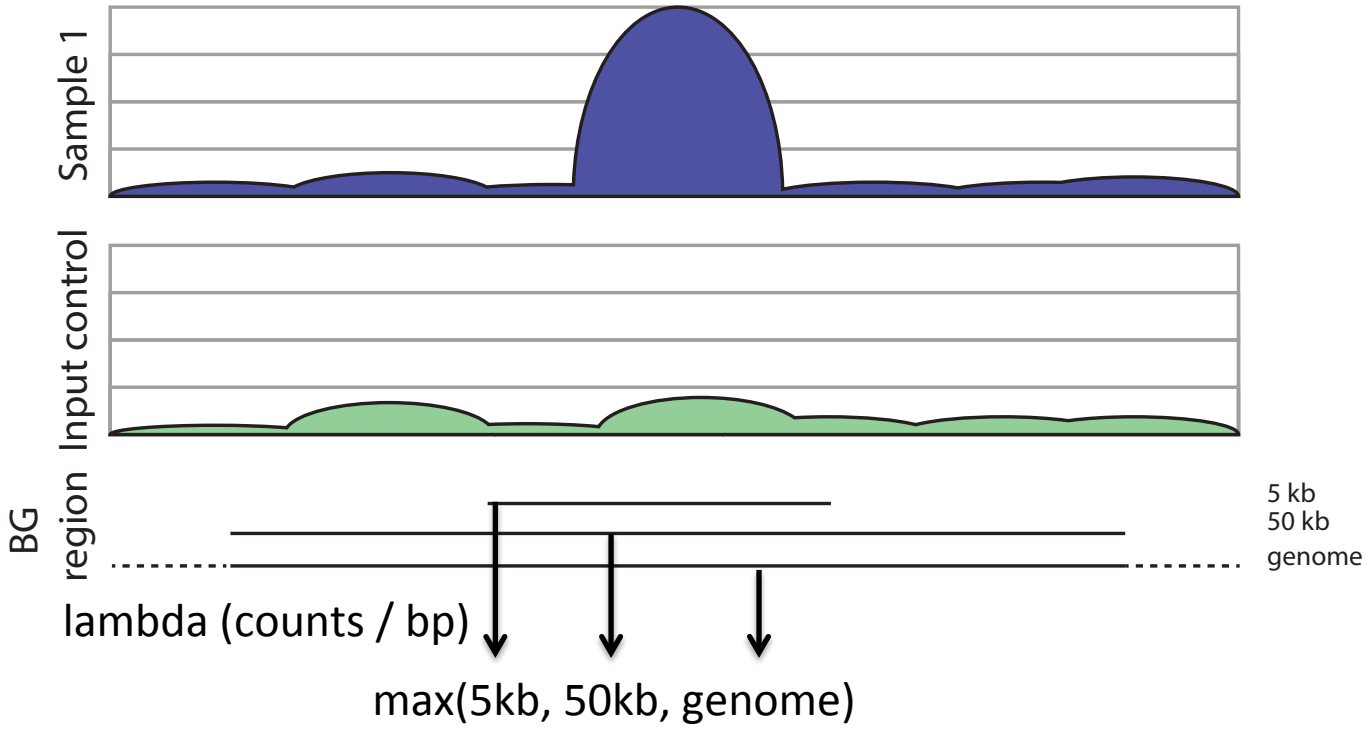


Coverage: how many fragments are aligned to each position?
Read counts: how many fragments start in each bin?

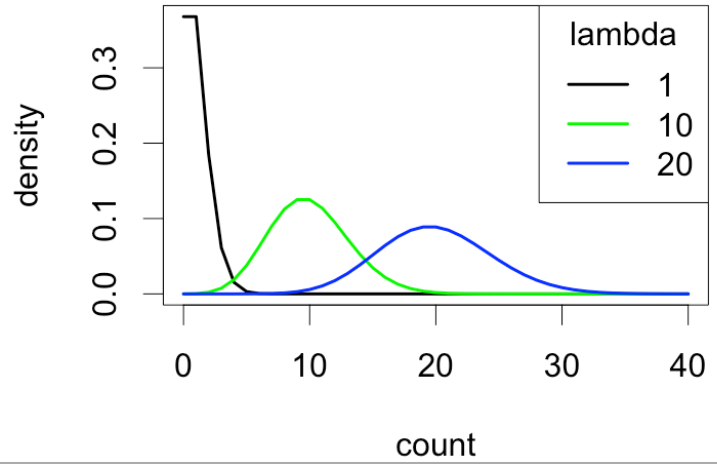
Peak calling strategies

- Statistical testing
  - Modeling the null (background) distribution
    e.g. MACS (Zhang 2008)
- Probabilistic modeling
  - Modeling the signal and the background distribution
    e.g. Zinba (Rashid 2011)
- Signal processing approaches
  - Filter
    e.g. Dfilter (Kumar 2013)

MACS



Poisson distribution



Probabilistic modeling: ZINBA

Typically NGS data show overdispersion (variance greater than Poisson lambda)

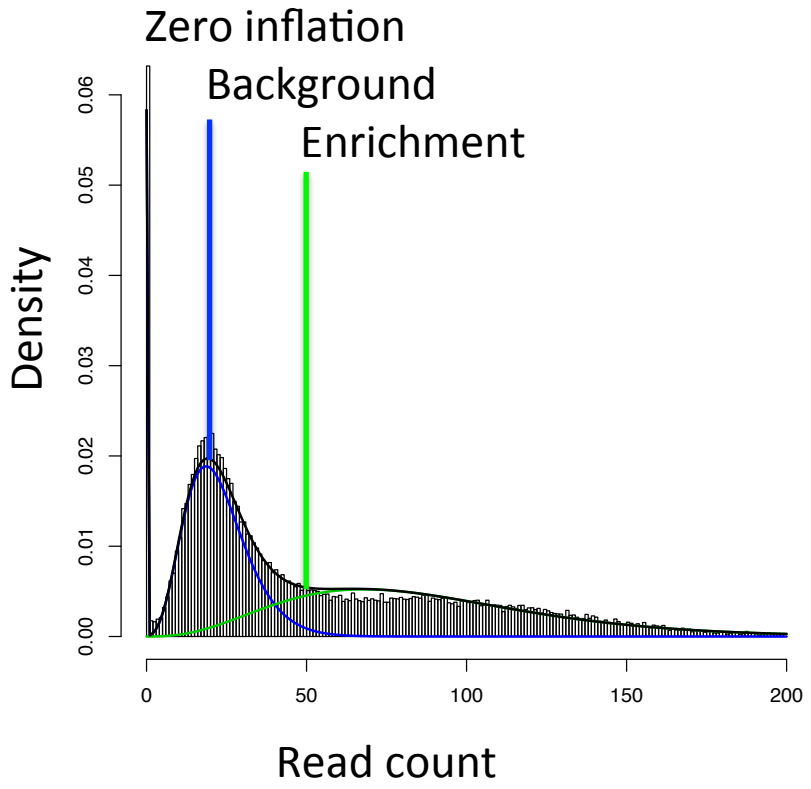
- Negative binomial distribution

Many empty bins distort estimation of background

- Zero inflation component

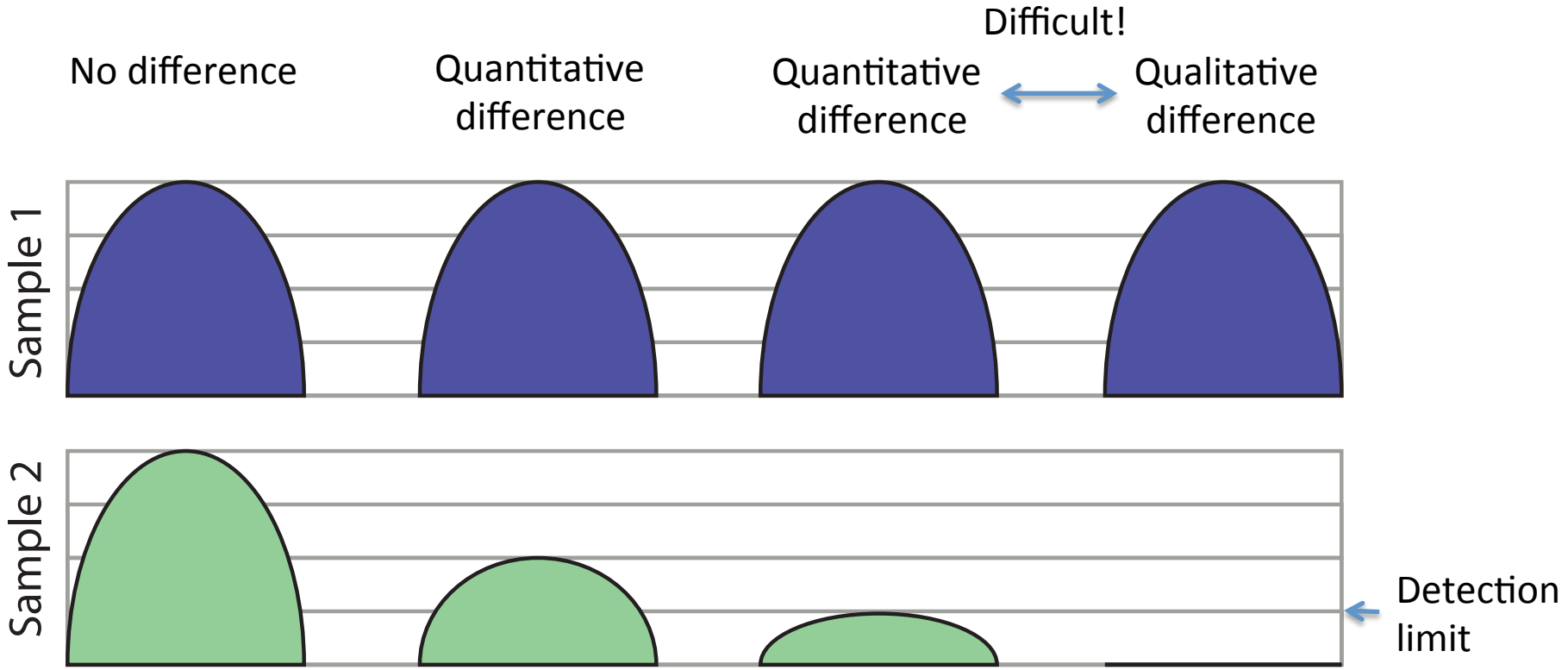
ZINBA (zero inflated negative binomial algorithm)

- 3 component mixture model



Comparison of epigenetic tracks

Goal: identify regions that differ between samples



Comparison of epigenetic tracks

Challenges:

- Actually two problems
  - Identification of features
  - Comparison of features
- Calling absence of peaks
- Use of input tracks?
- No gold standard for the evaluation of methods

Strategies

Where to look?

- Independent peak detection analyses
- Sliding window approaches
- Binning

How to compare?

- Comparison absence / presence of calls
- Quantitative comparison
- Normalization
- Hypothesis testing
- Probabilistic modeling
- Considering local dependencies

Available tools (selection)

Tool		Diffbind	PePr	diffReps	RSEG	Chipdiff	histoneHMM
where to look	peak detection	✓	✗	prescreening	✗	prescreening	✗
	sliding window	✗	✓	✓	✗	✗	✗
	binning	✗	✗	✗	✓	✓	✓
how to compare	use of input	✗	substract input	✗	✗	✗	✗
	normalization	scaling	scaling	scaling	✗	✗	✗
	hypothesis testing	negative binomial	negative binomial	negative binomial	✗	✗	✗
	probabilistic	✗	✗	✗	NBDiff	Hierarchical binomial model	Multivariate NB
	dependencies	✗	merging	merging, hotspot detection	HMM	HMM	HMM

METHOD

histoneHMM: Differential analysis of histone modifications with broad genomic footprints

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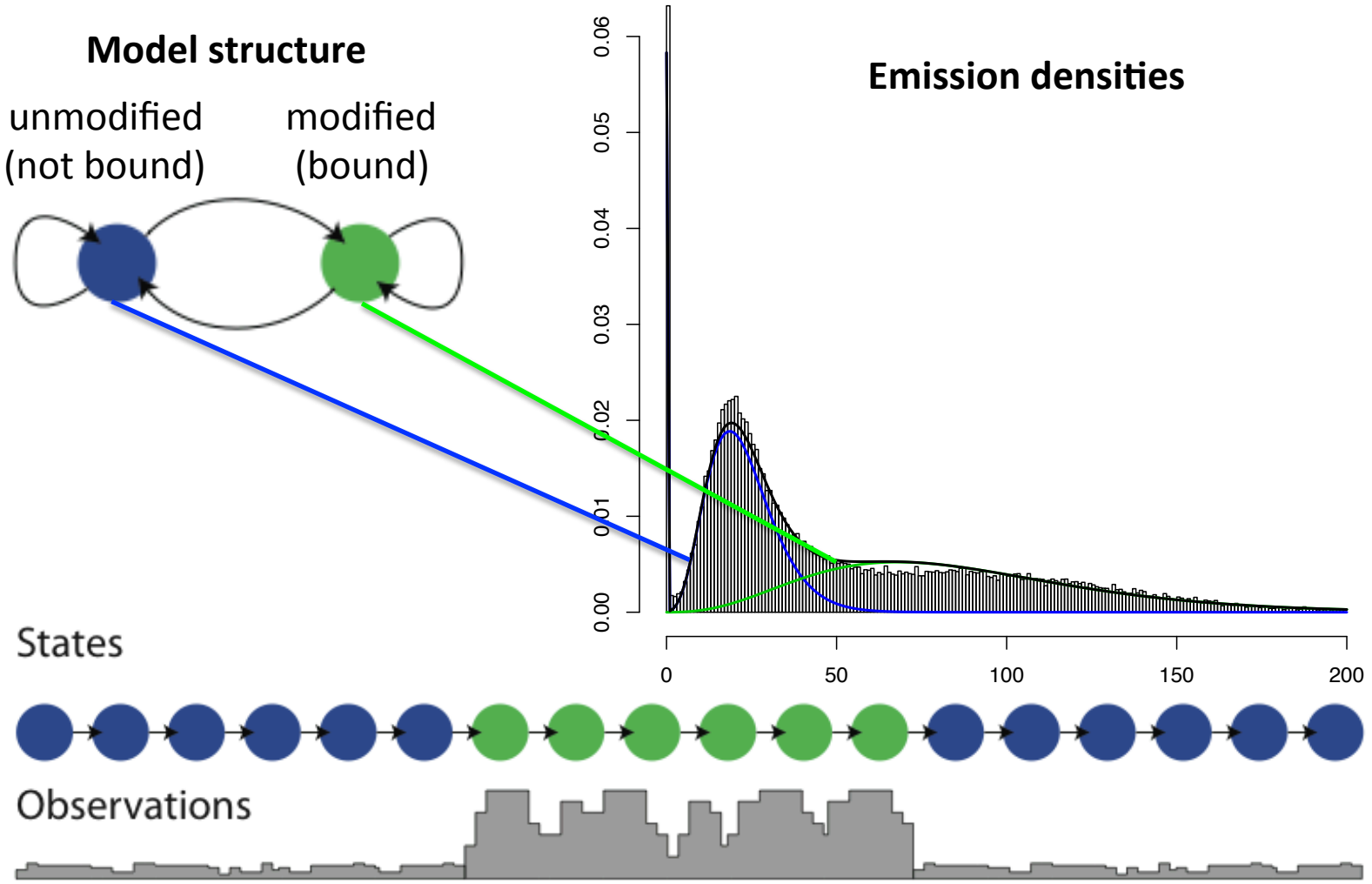
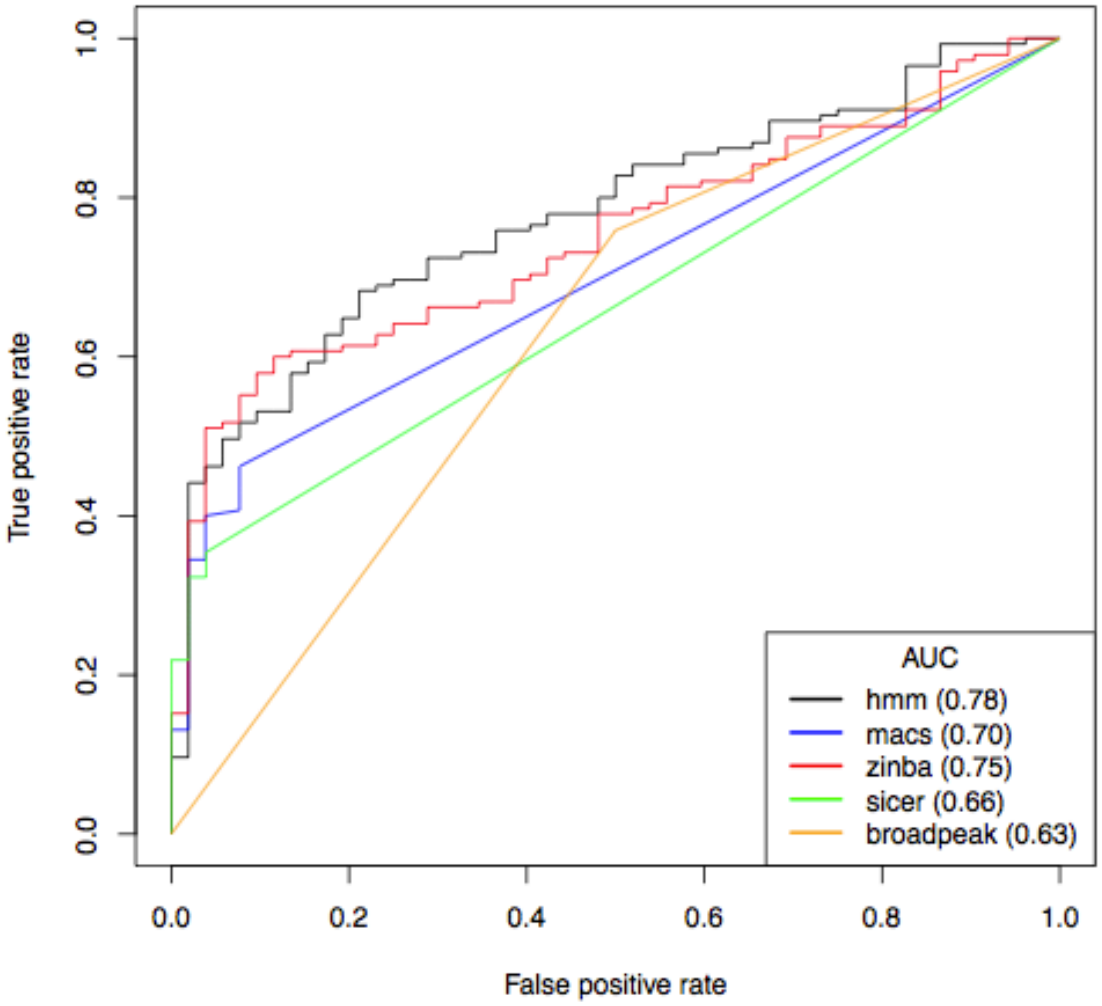
HMM for region calling

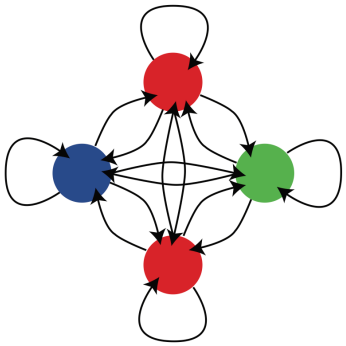


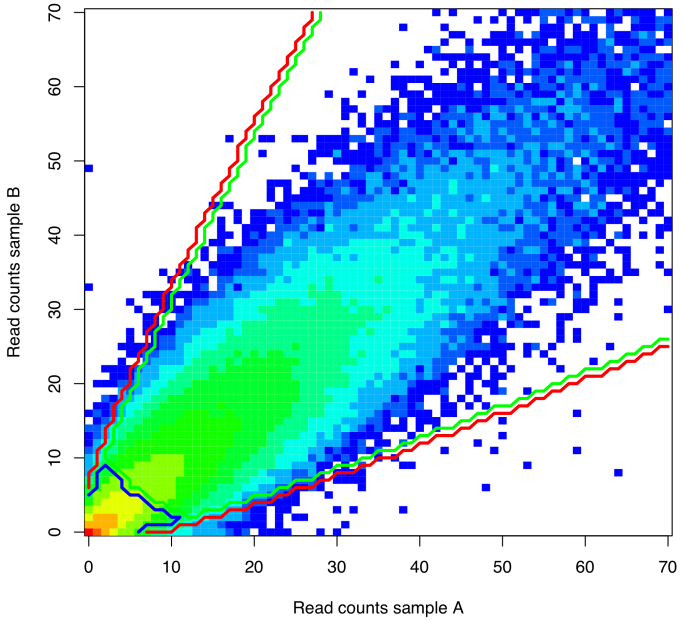
Evaluation with qPCR data

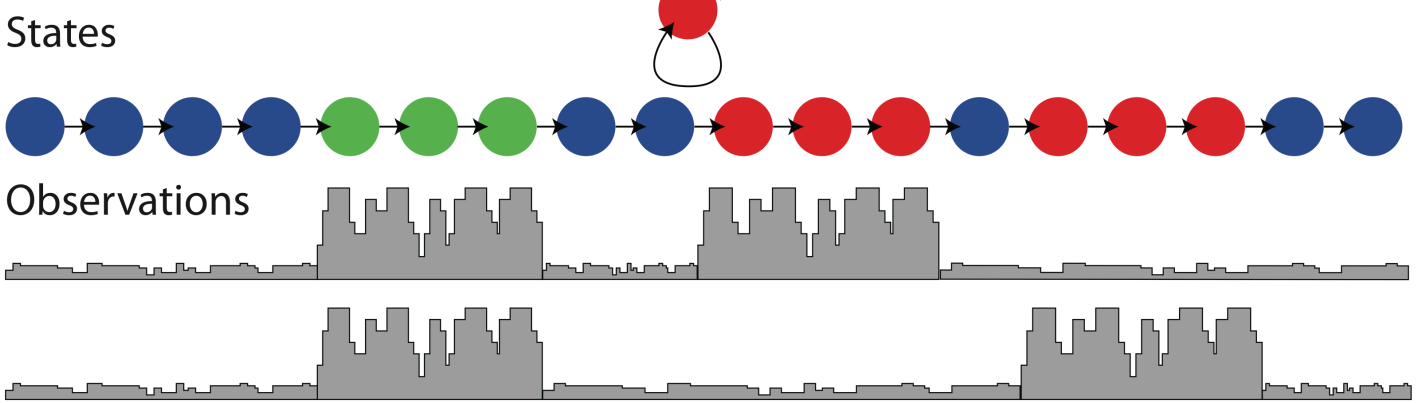


HMM for differential analysis

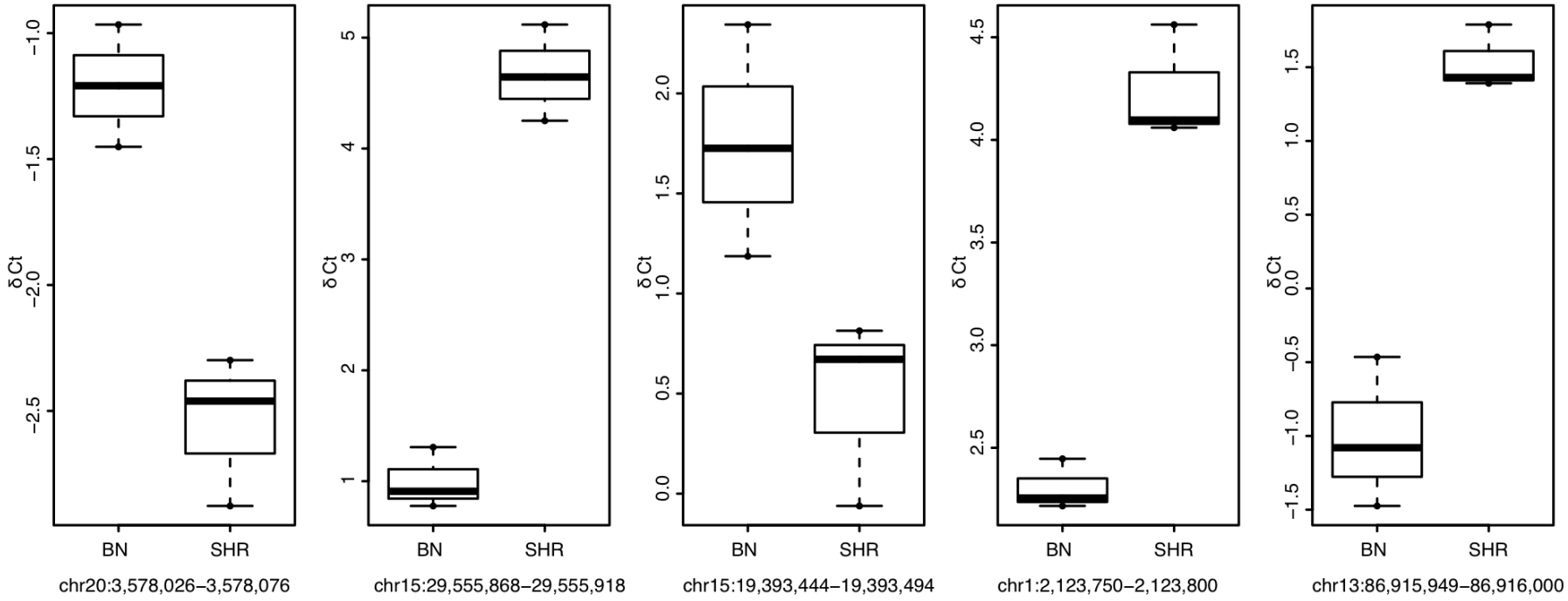
Hidden Markov model for multivariate count data







Evaluation with qPCR data



Evaluation with expression data