Simple statistical models for complex 3D genome data

Barcelona, 1 February 2019

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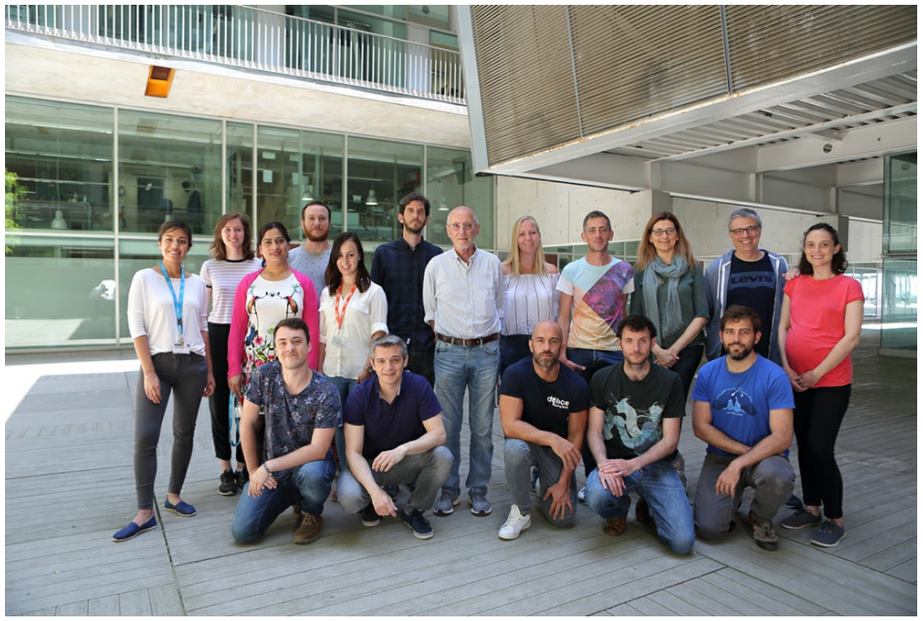
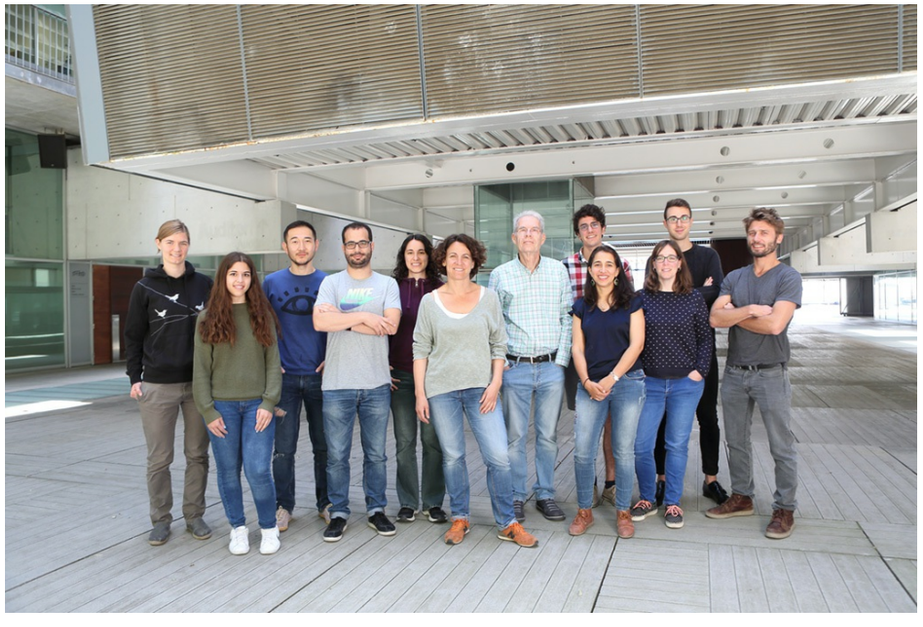
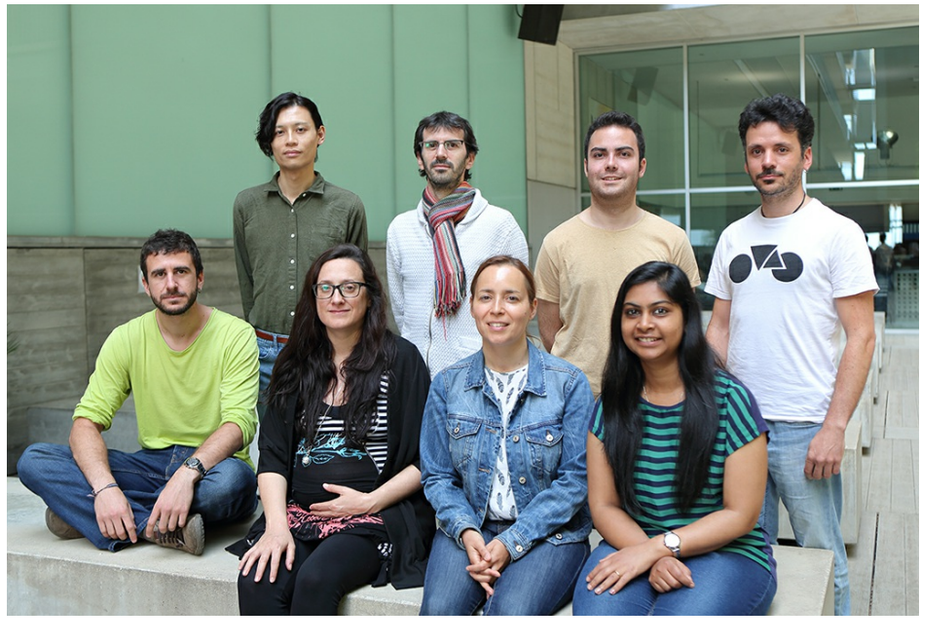
4DGenome

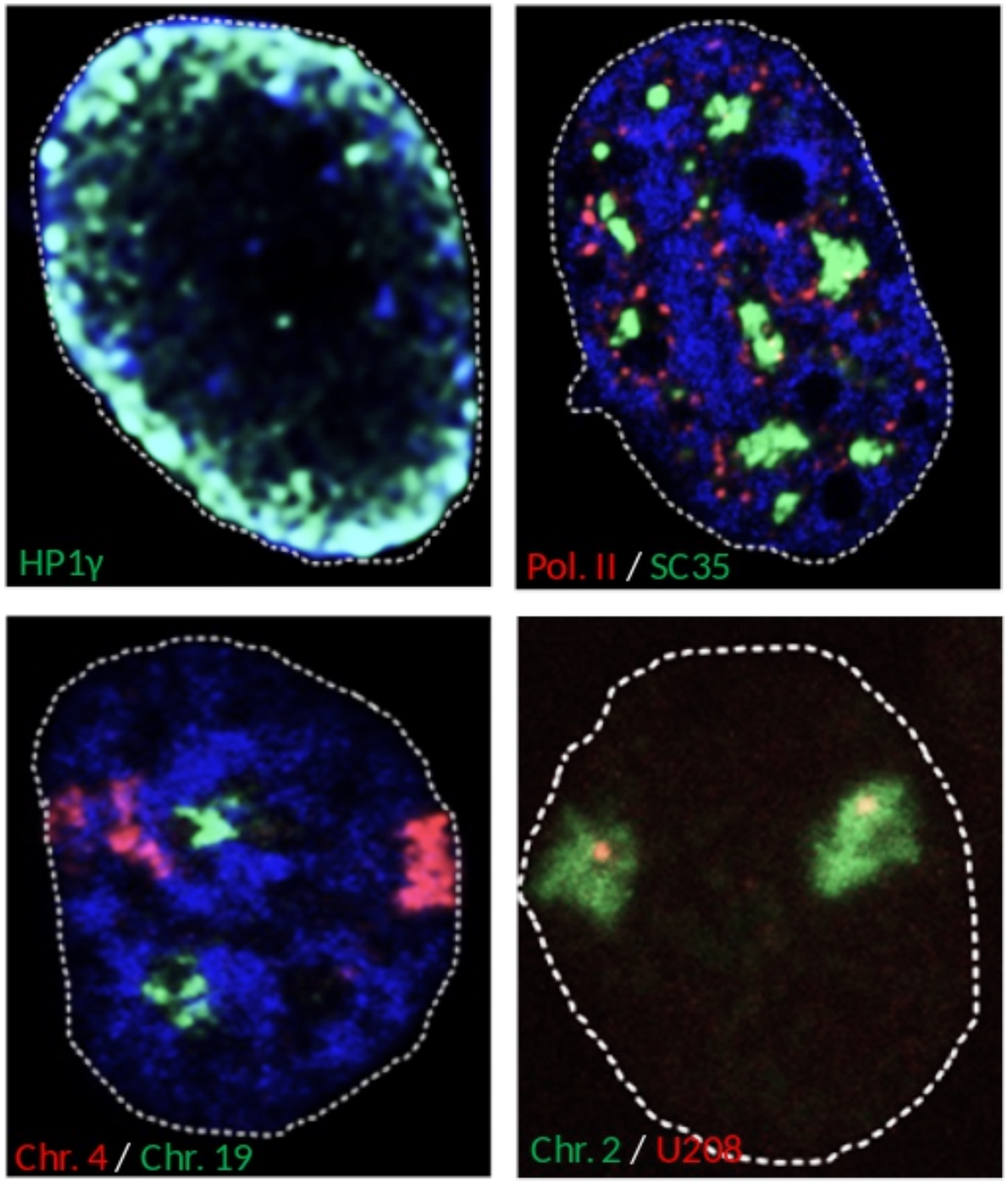






Motivation

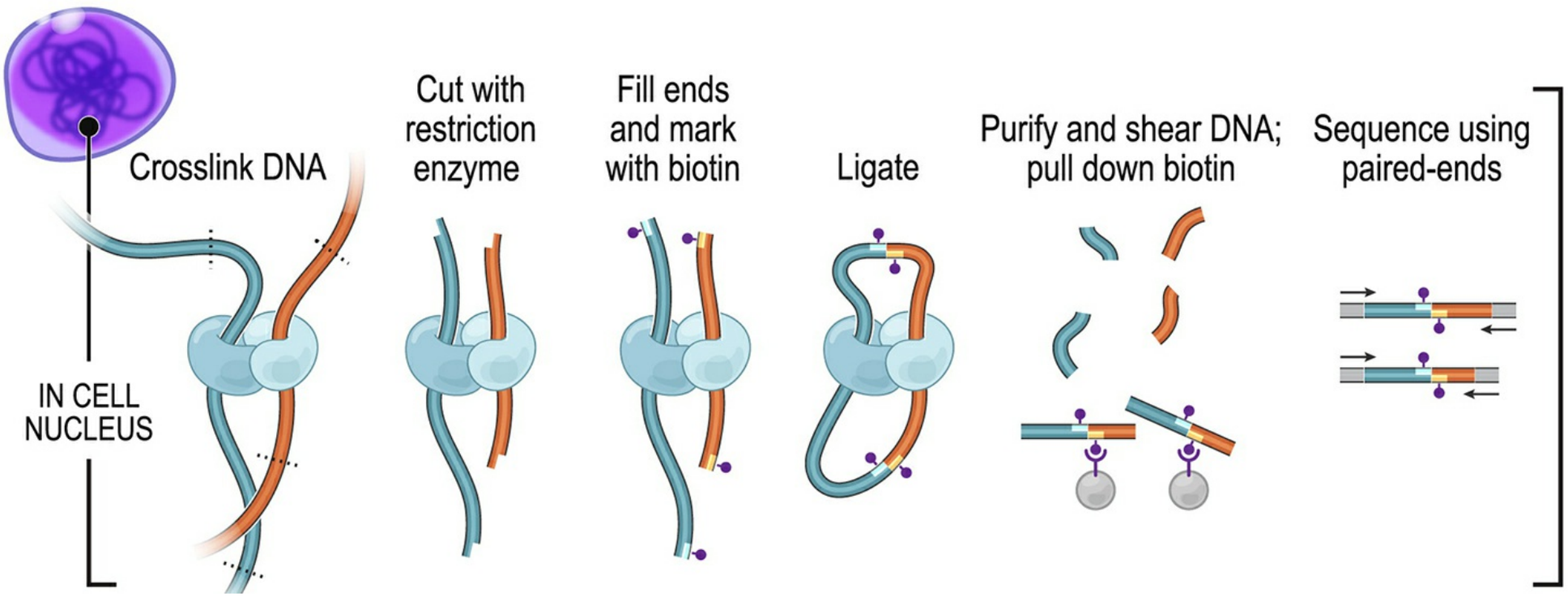
Genome structure is not random



Chromosome conformation capture

Dekker, J. et al. (2002)

Science

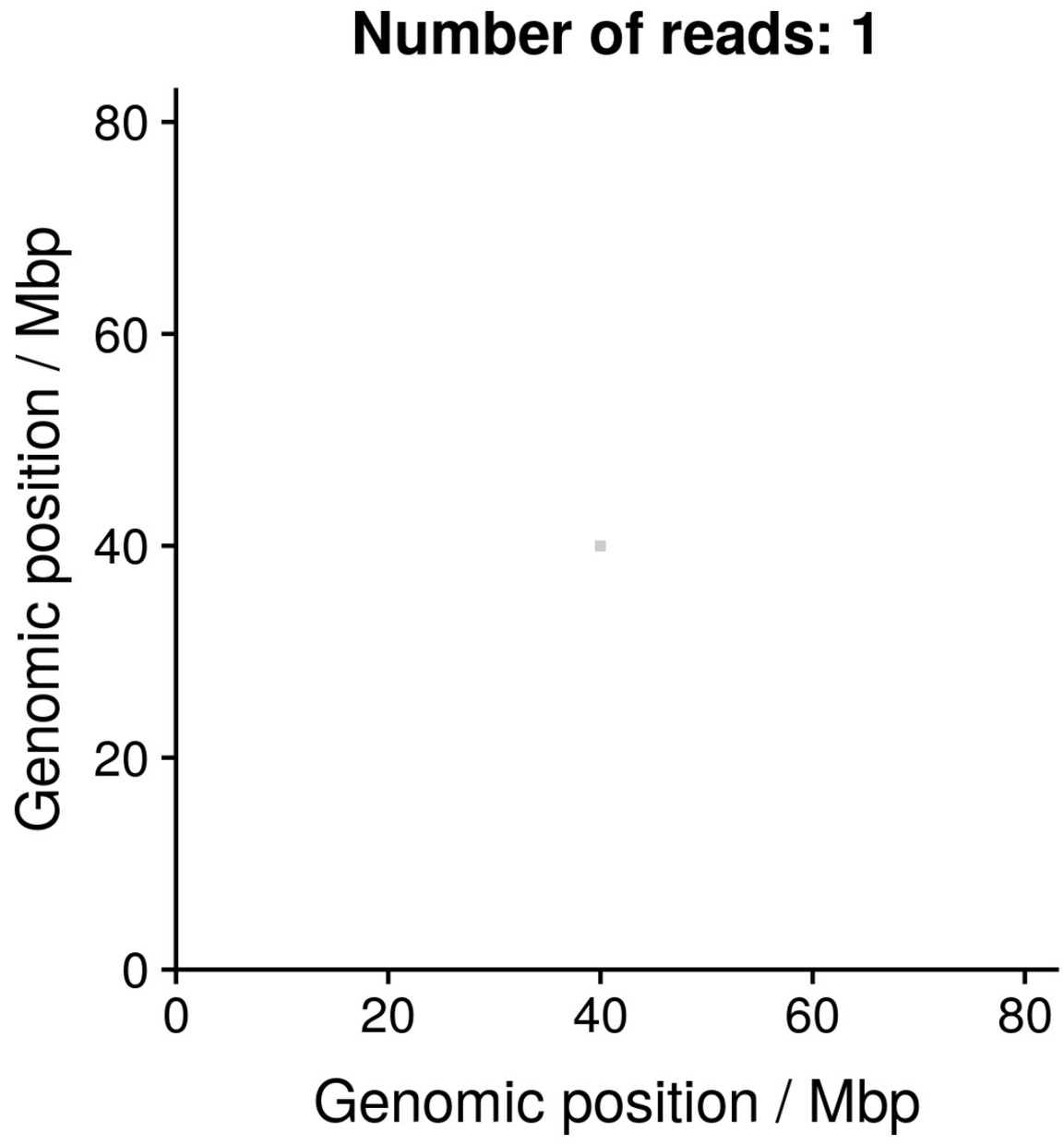


Lieberman-Aiden, E. et al. (2009)

Science

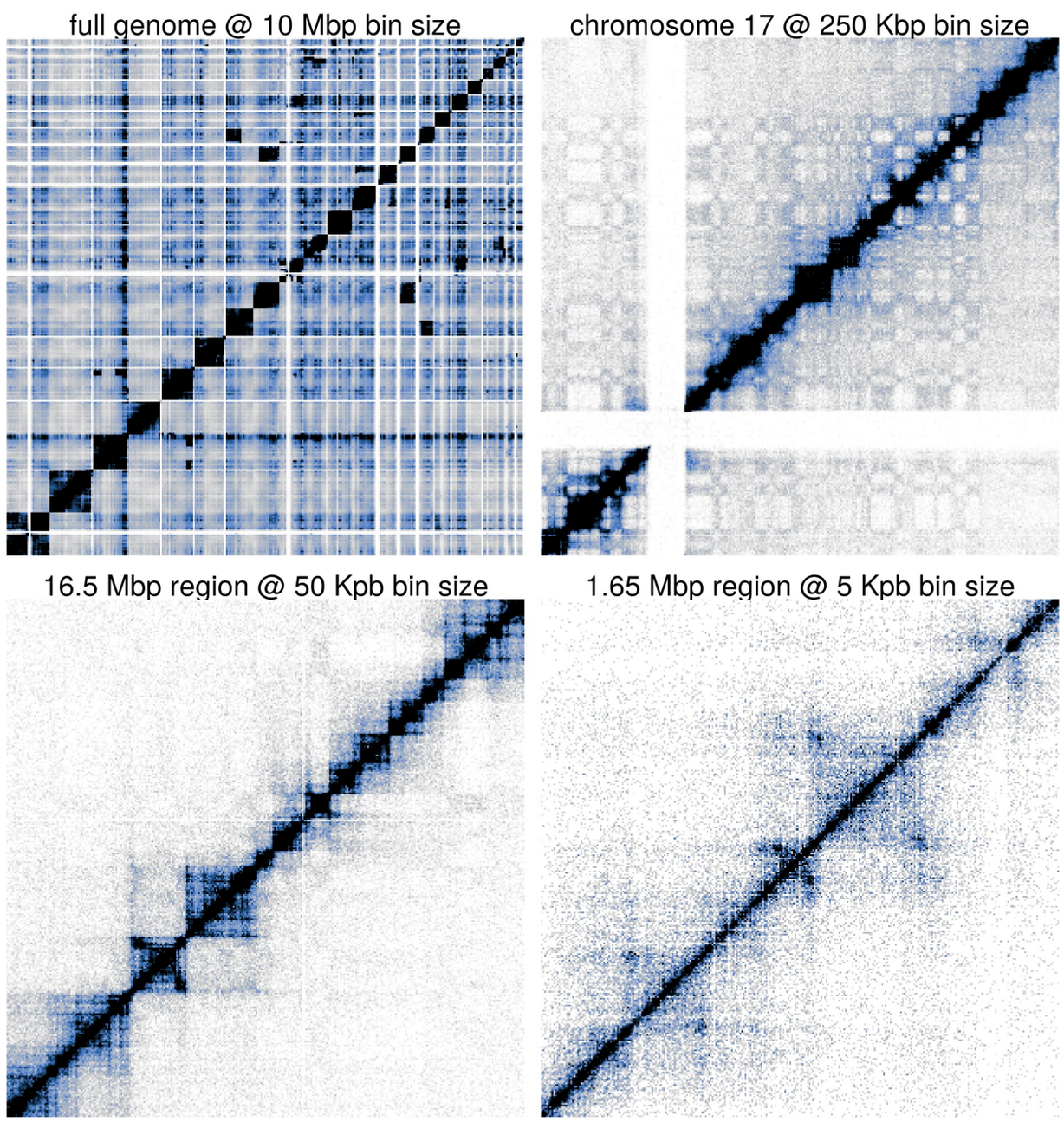
Hi-C matrix

Step by step


Number of reads: 1
Genomic position / Mbp
0
20
40
60
80
Genomic position / Mbp

What does Hi-C offer?

Territories, compartments, domains, loops



Biases

Genomic features affect Hi-C

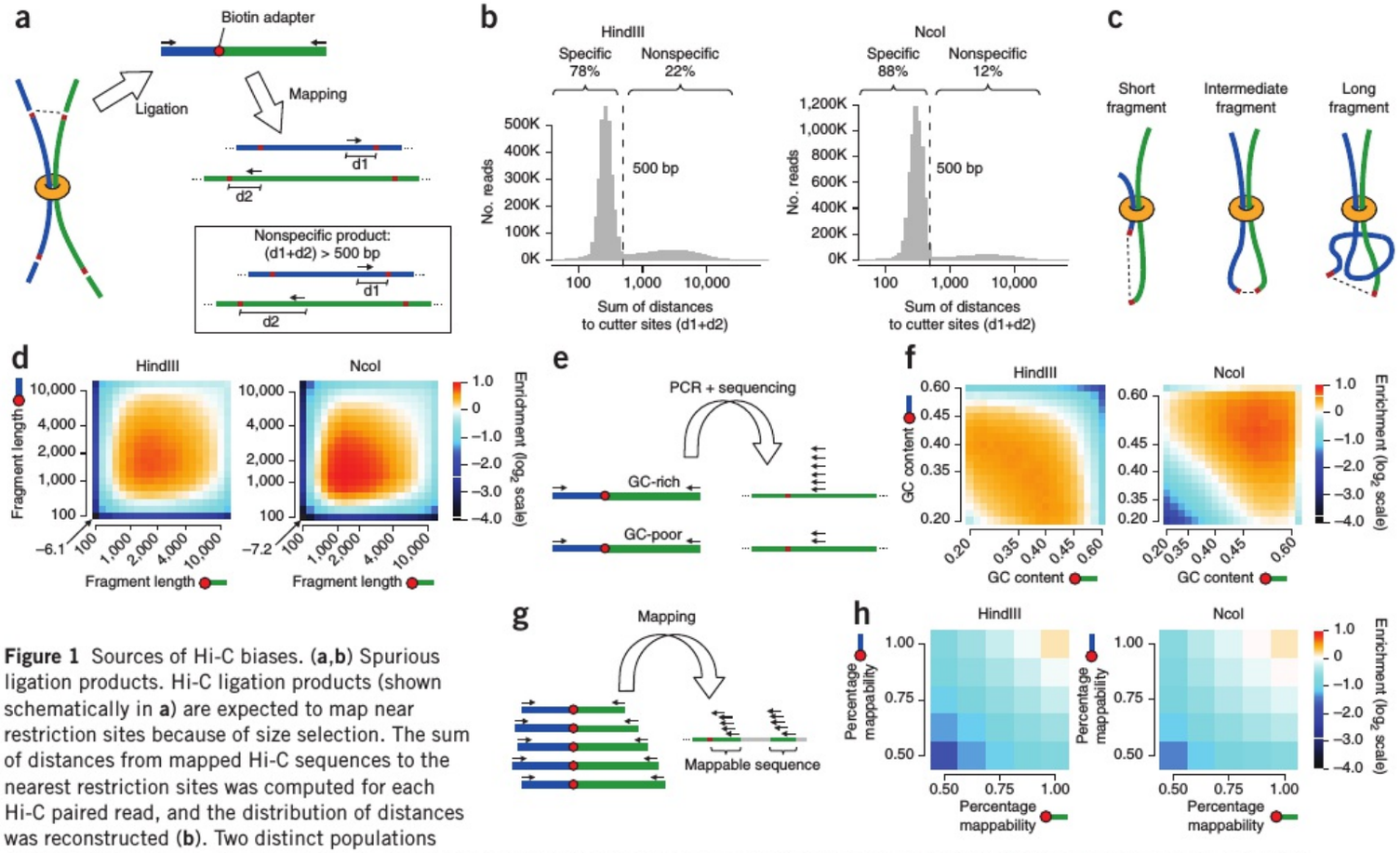


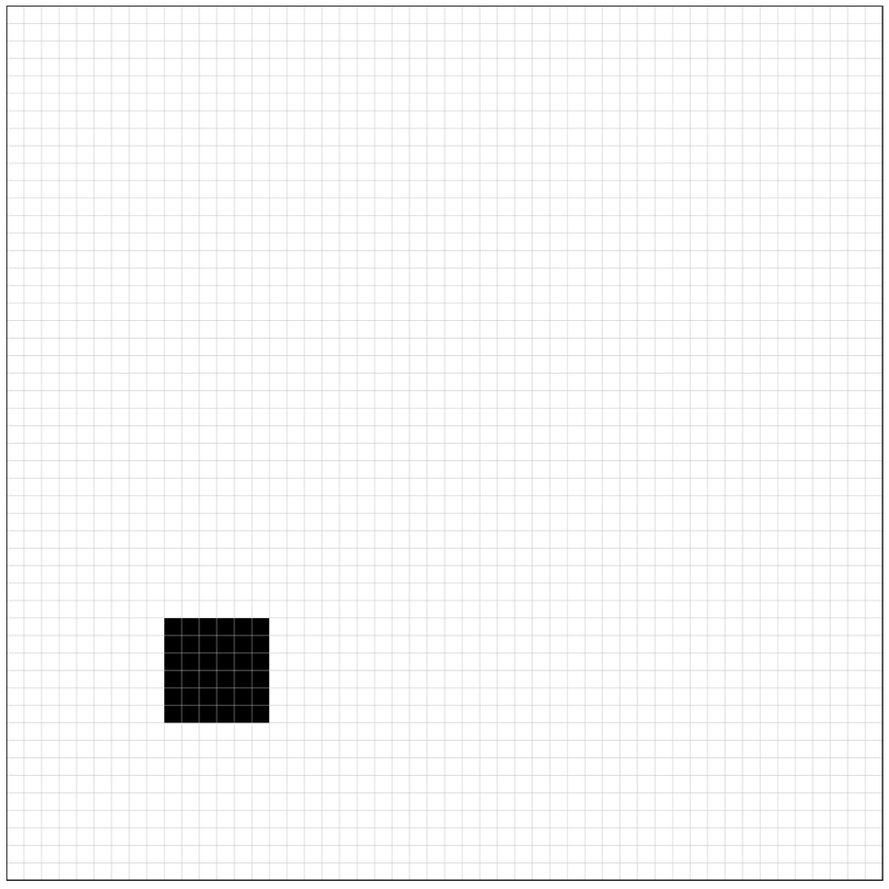
Figure 1 Sources of Hi-C biases. (**a**,**b**) Spurious ligation products. Hi-C ligation products (shown schematically in **a**) are expected to map near restriction sites because of size selection. The sum of distances from mapped Hi-C sequences to the nearest restriction sites was computed for each Hi-C paired read, and the distribution of distances was reconstructed (**b**). Two distinct populations of reads are observed, one distributed as expected for normally ligated and size-selected products (HindIII 78%, NcoI 88%) and one including reads mapped farther away from restriction sites. (**c**,**d**) Fragment lengths and ligation efficiency. Restriction fragments of different lengths are shown schematically in **c** and can be hypothesized to affect crosslinking and ligation efficiency. The *trans* Hi-C coverage enrichment is defined as the ratio between the observed number of *trans* contacts and the total number of assayed fragment pairs. Shown are coverage enrichments for all of the fragment ends, binned into 20 equal-sized bins according to fragment length (*x* and *y* axes). Similar trends are observed for the HindIII and NcoI experiments. (**e**,**f**) Local GC content and Hi-C coverage. Ligation product processing and sequencing may be biased by GC content (**e**). *Trans*-contact enrichments (**f**) stratified according to the GC content of the 200 bp near the restriction fragment ends show intense and contrasting GC biases for the HindIII and NcoI experiments. (**g**,**h**) Effect of sequence uniqueness. Different fractions of uniquely mappable short tags are observed next to restriction sites (**g**). As shown in **h**, this has a direct empirical linear effect on Hi-C coverage.

Yaffe, E. and Tanay, A. (2011)

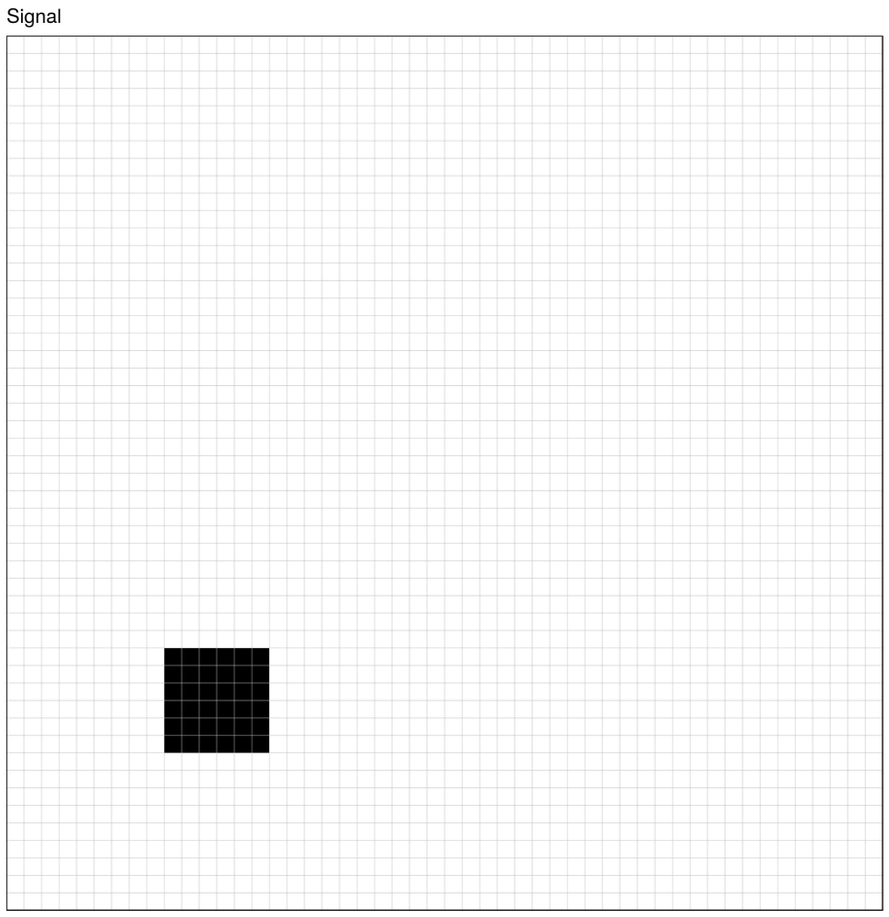
Nature genetics

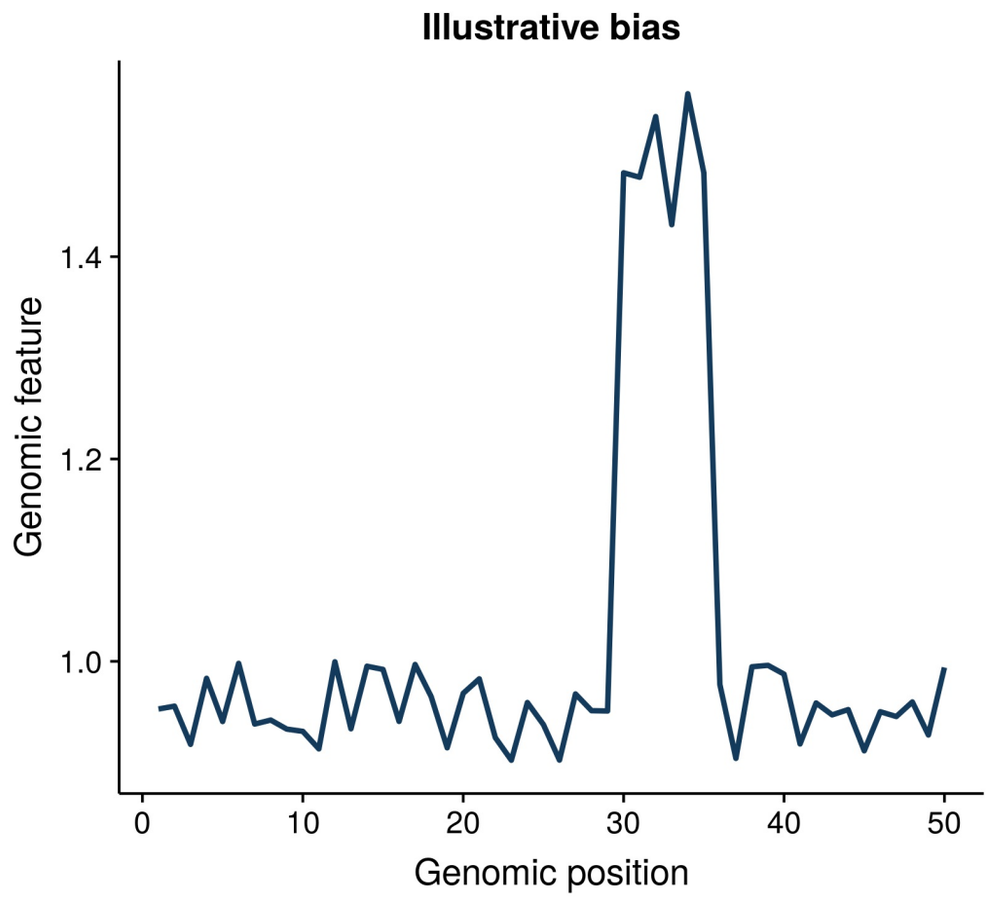
Illustrating biases

Signal



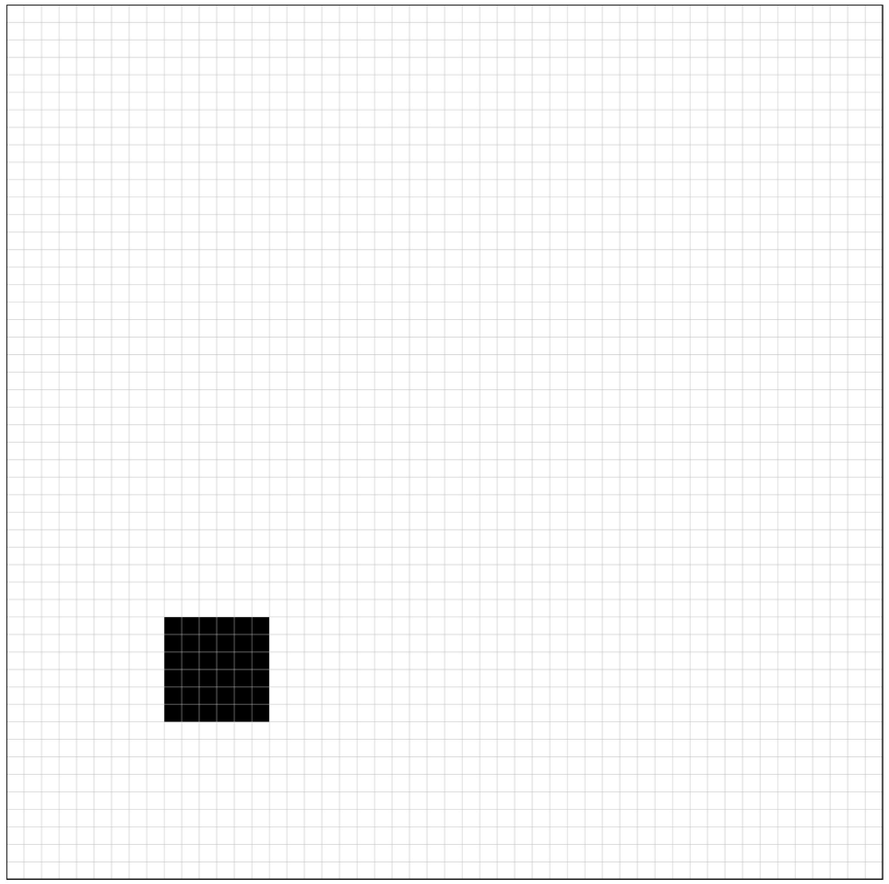
Illustrating biases



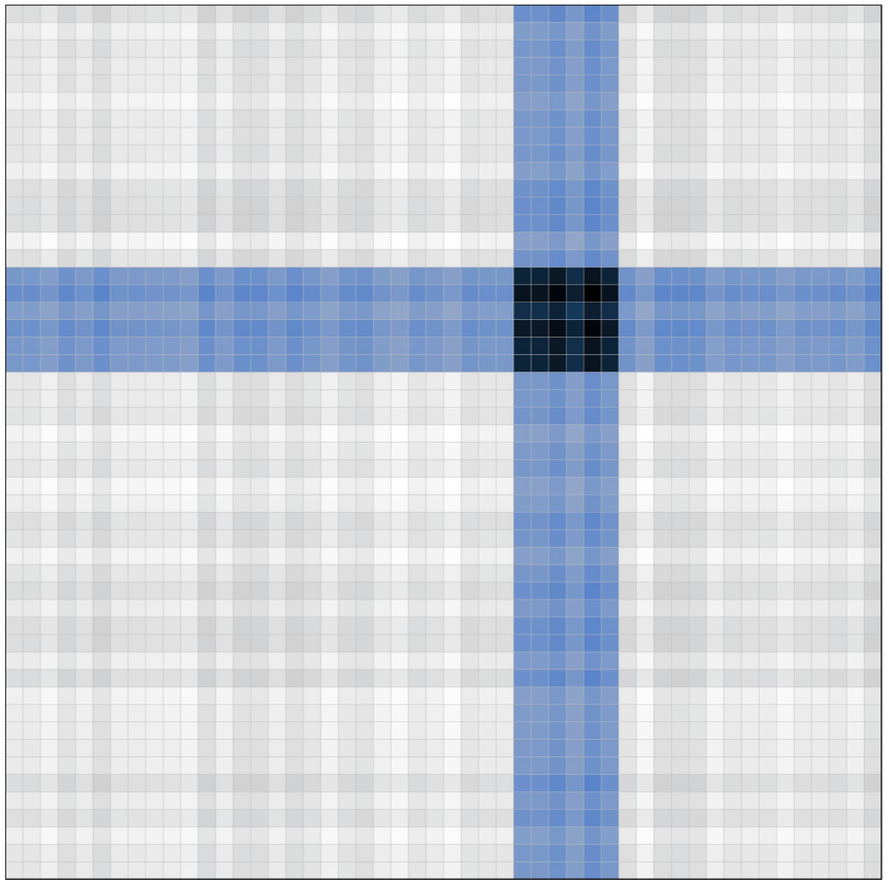


Illustrating biases

Signal

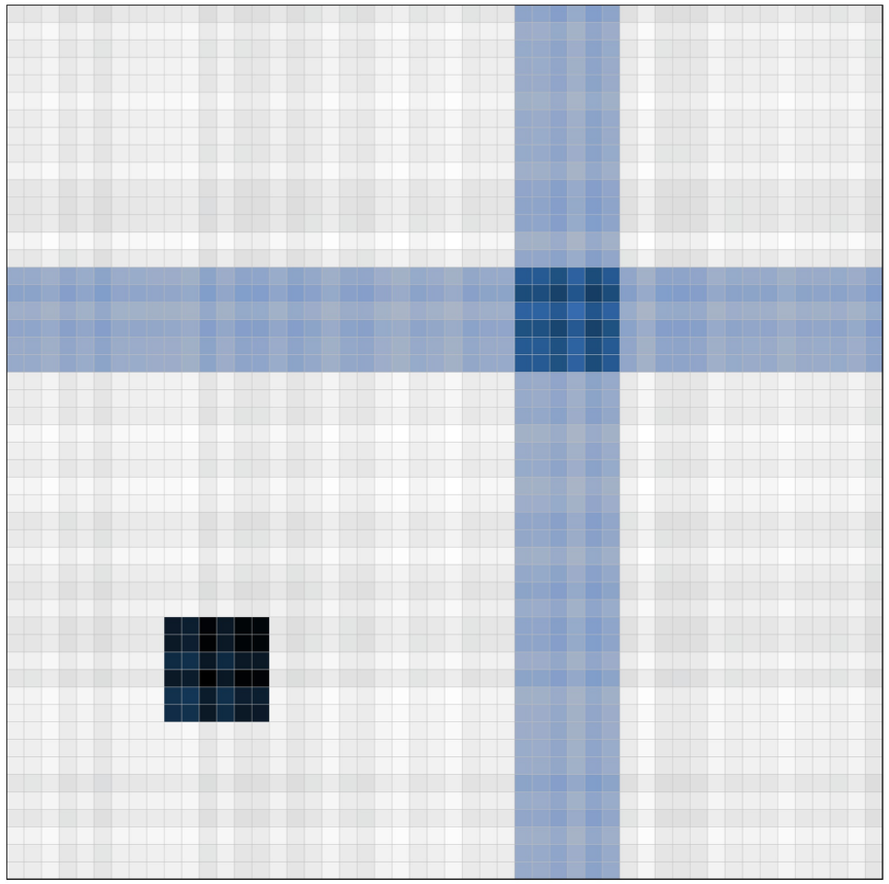


Bias

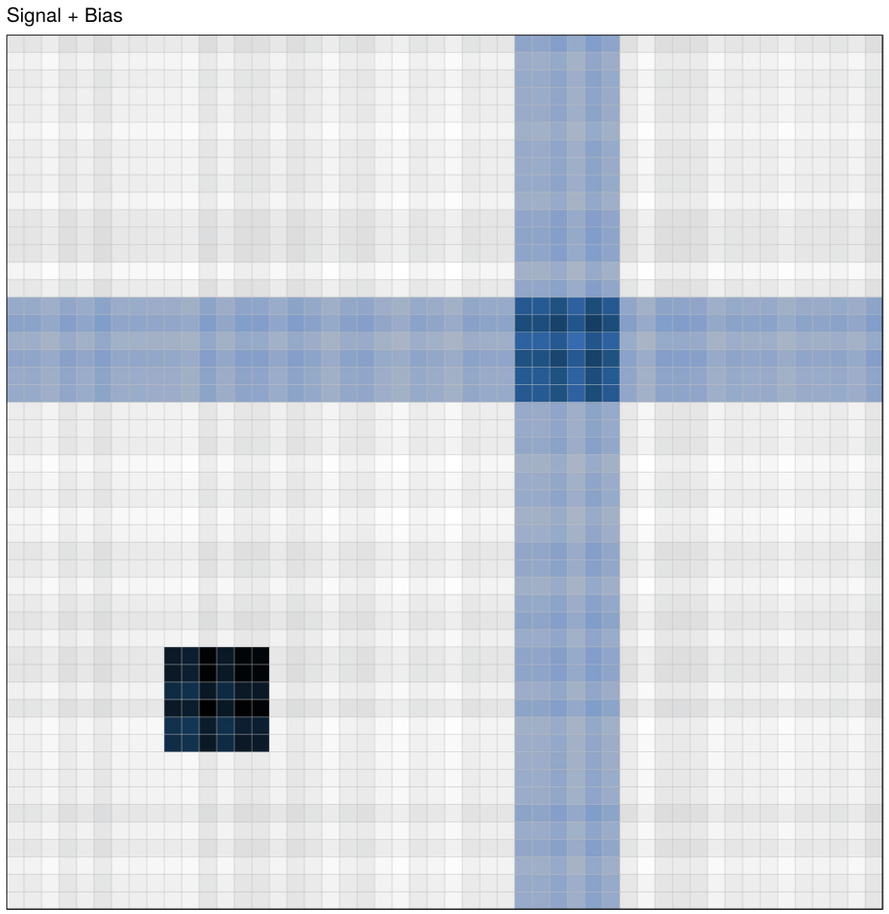


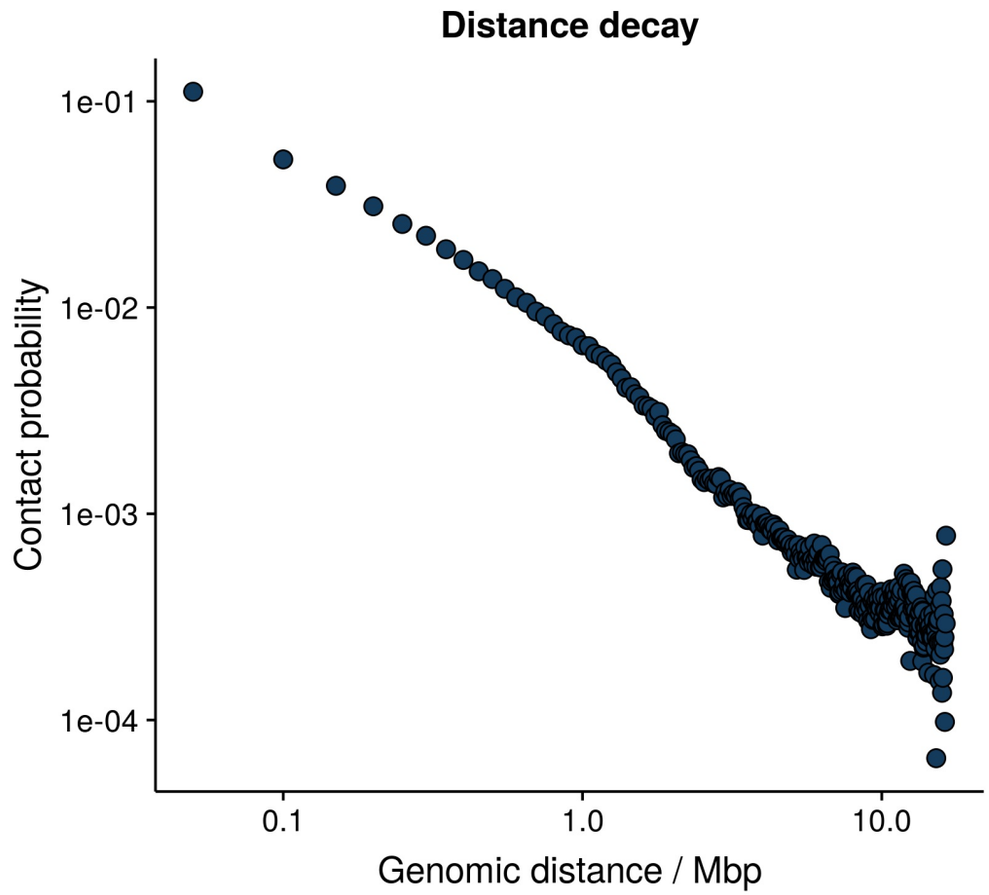
Illustrating biases

Signal + Bias



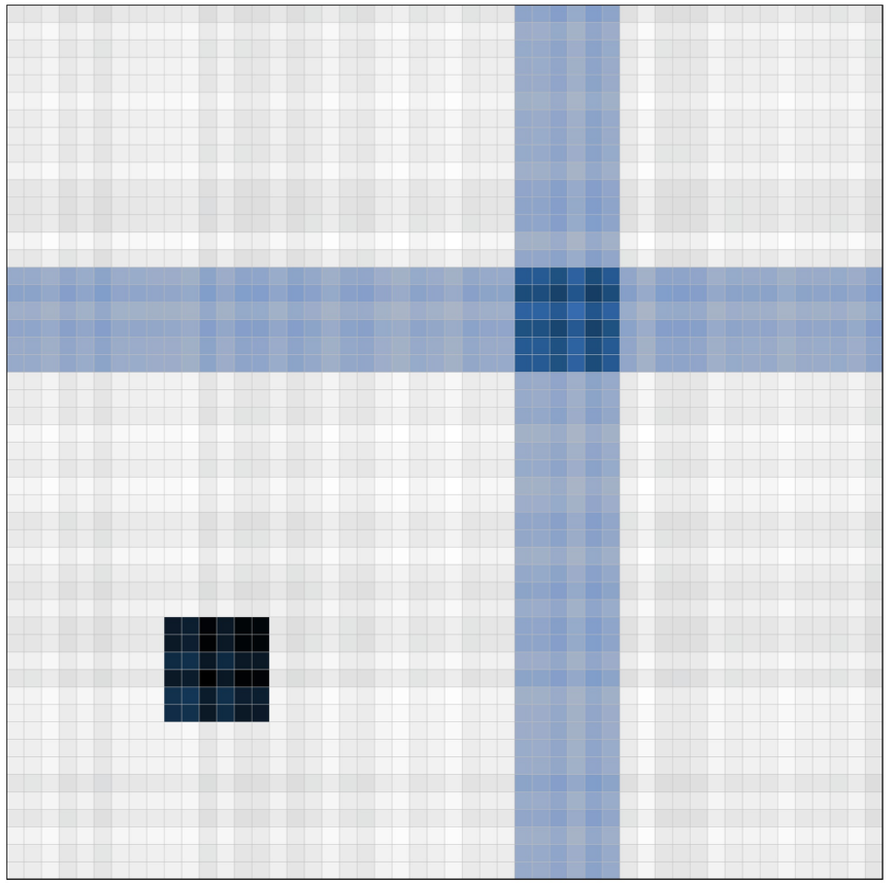
Illustrating biases



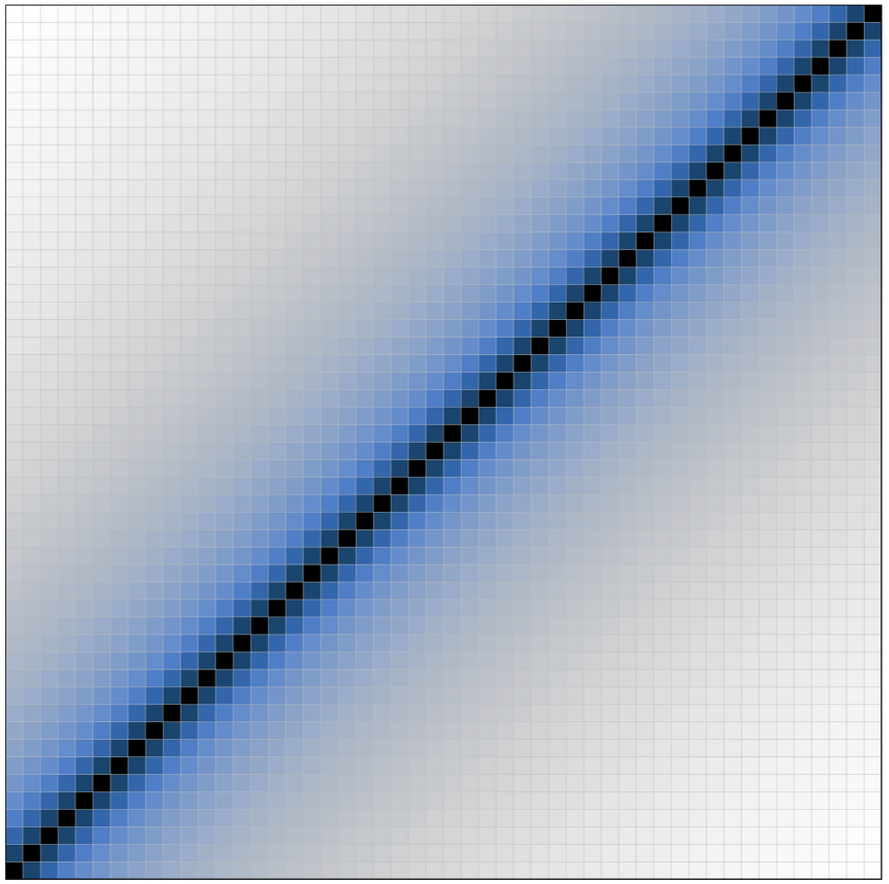


Illustrating biases

Signal + Bias

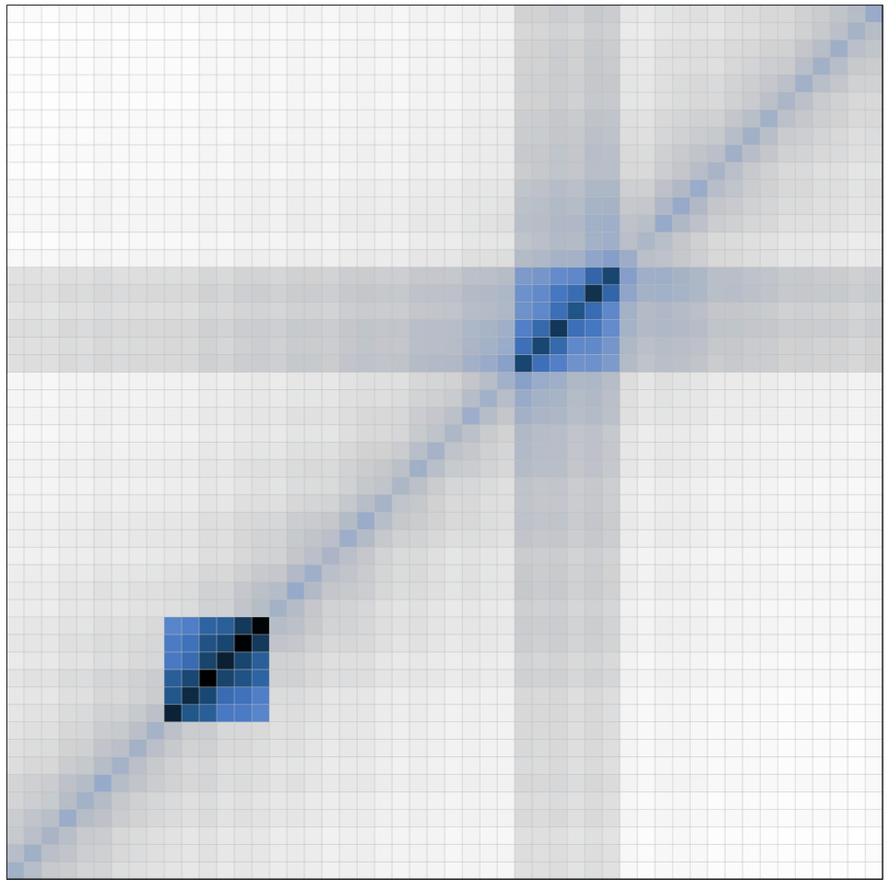


Decay



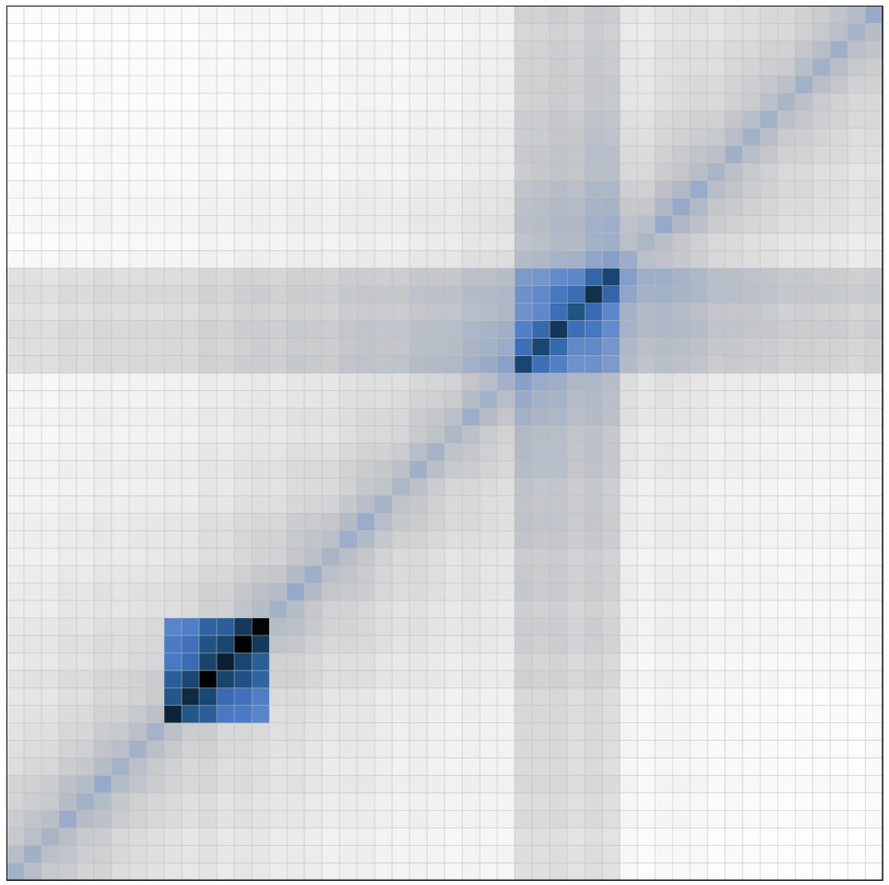
Illustrating biases

Signal + Bias + Decay

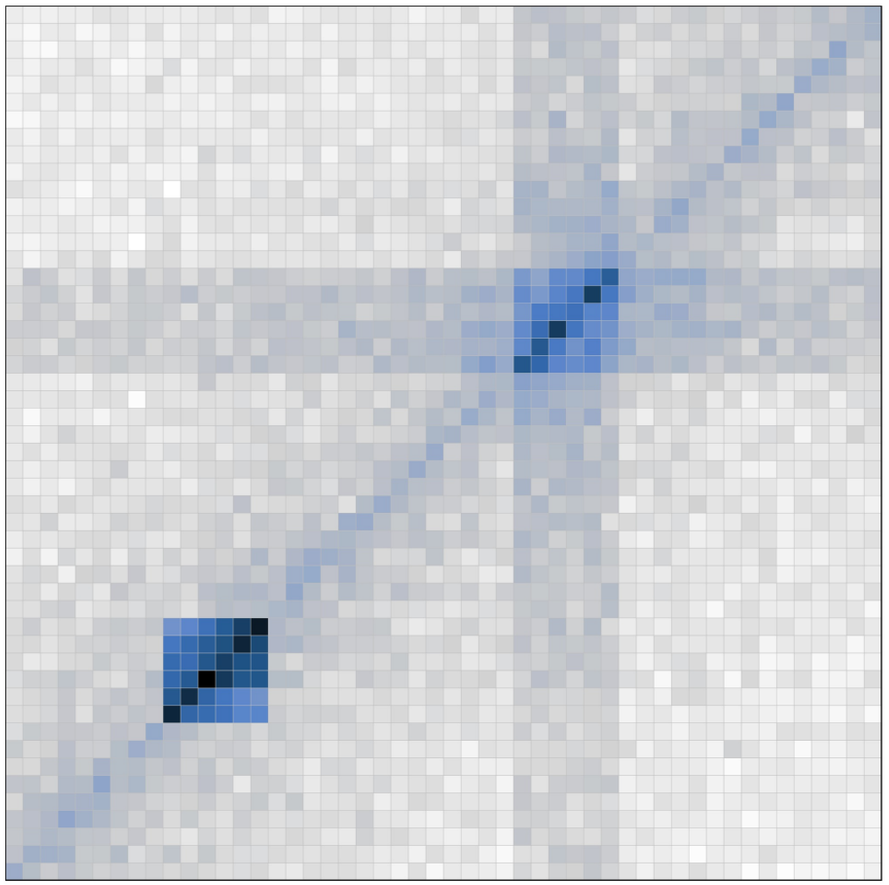


Illustrating biases

Signal + Bias + Decay

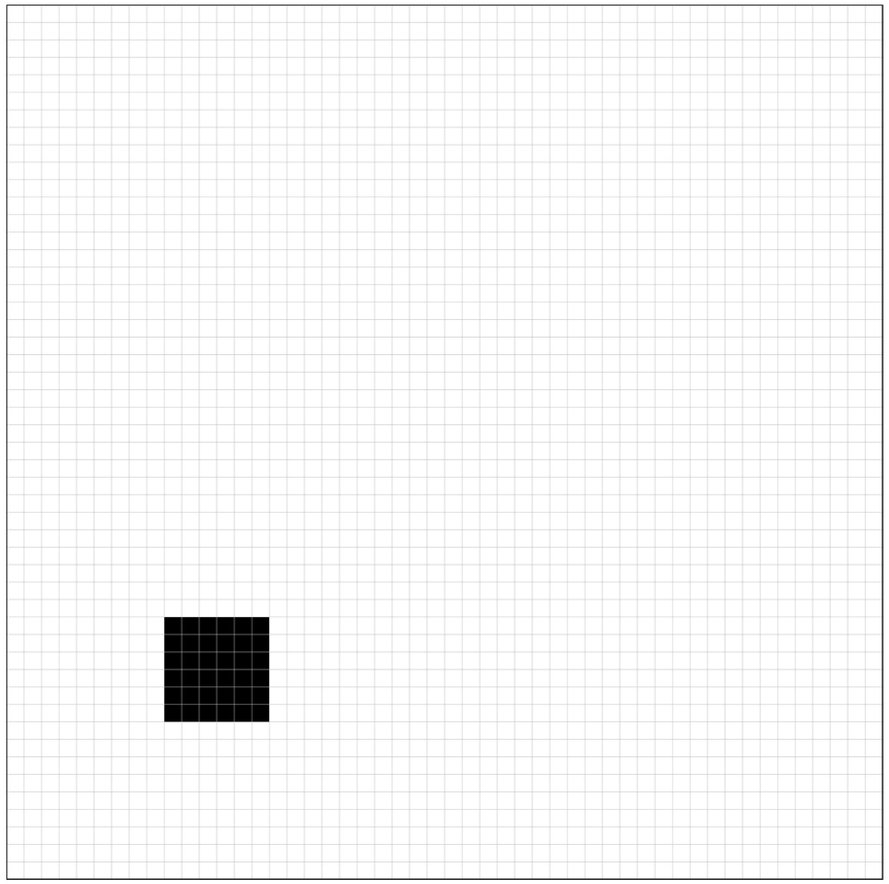


Signal + Bias + Decay + Noise

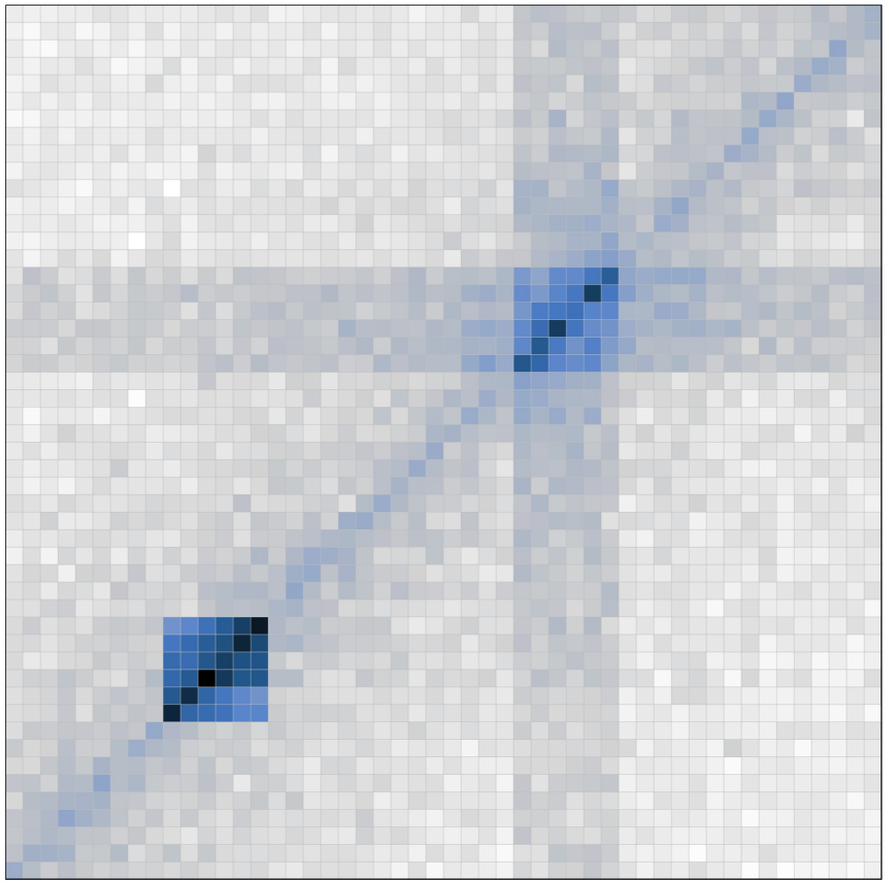


Illustrating biases

Signal



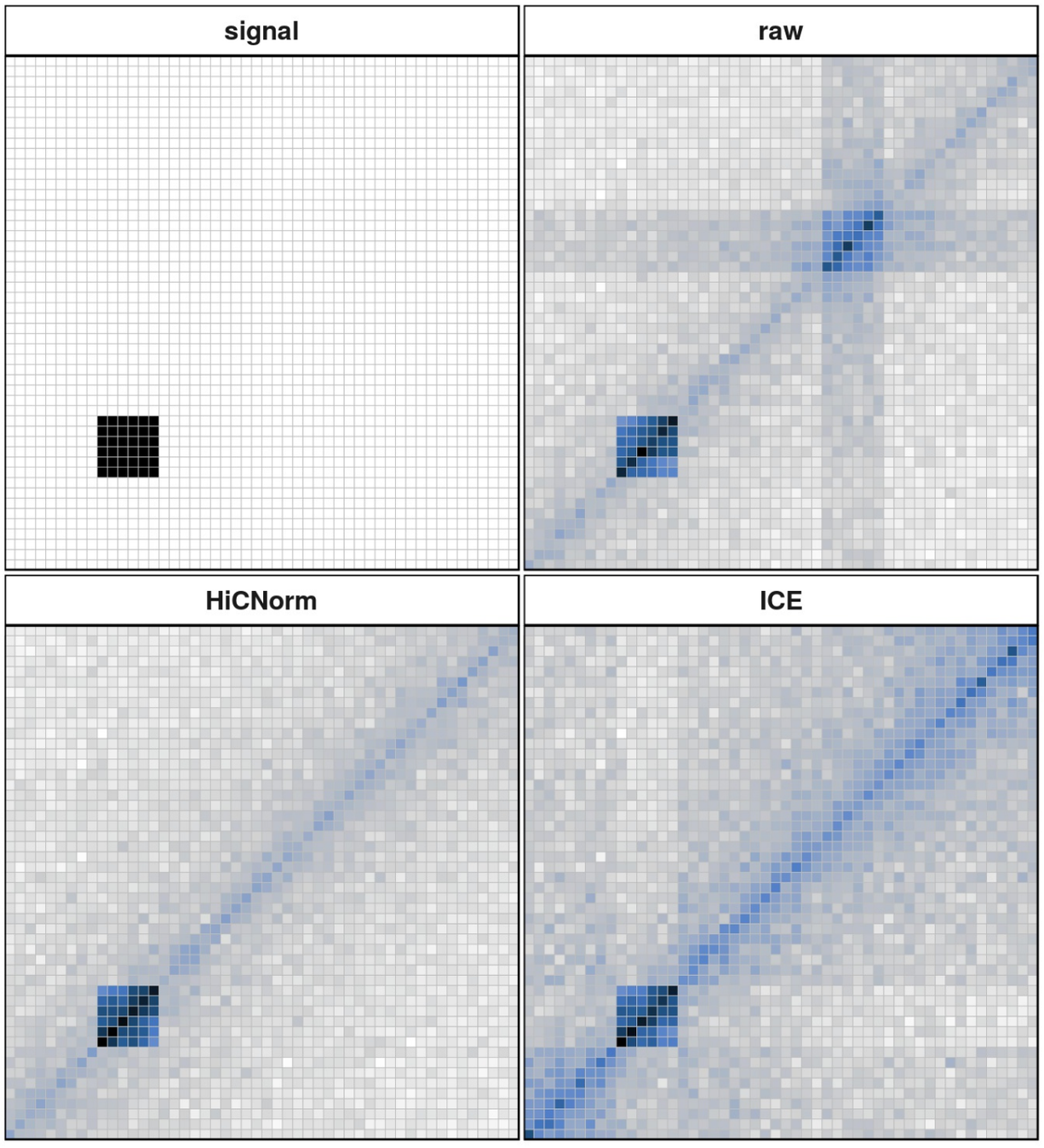
Signal + Bias + Decay + Noise



Previous approaches

HiCNorm	ICE
Explicit model of biases	Implicit correction
Regression model	Matrix balancing
All matrix entries	Equal visibility
Yaffe, E. and Tanay, A. (2011)	**Imakaev, M. et al. (2012)**
Nature genetics	Nature methods
Hu, M. et al. (2012)	
Bioinformatics	

In action



HiCNorm

✓ fewer artifacts

✗ very slow

✗ no high resolution

ICE

✗ more artifacts

✓ fast

✓ high resolution

HiCNorm

✓ fewer artifacts

✗ very slow

✗ no high resolution

ICE

✗ more artifacts

✓ fast

✓ high resolution

✗ aberrant karyotypes

Wish list

Wish list

♡ Suitable aberrant karyotypes

Wish list

♡ Suitable aberrant karyotypes

♡ As good as existing

Wish list

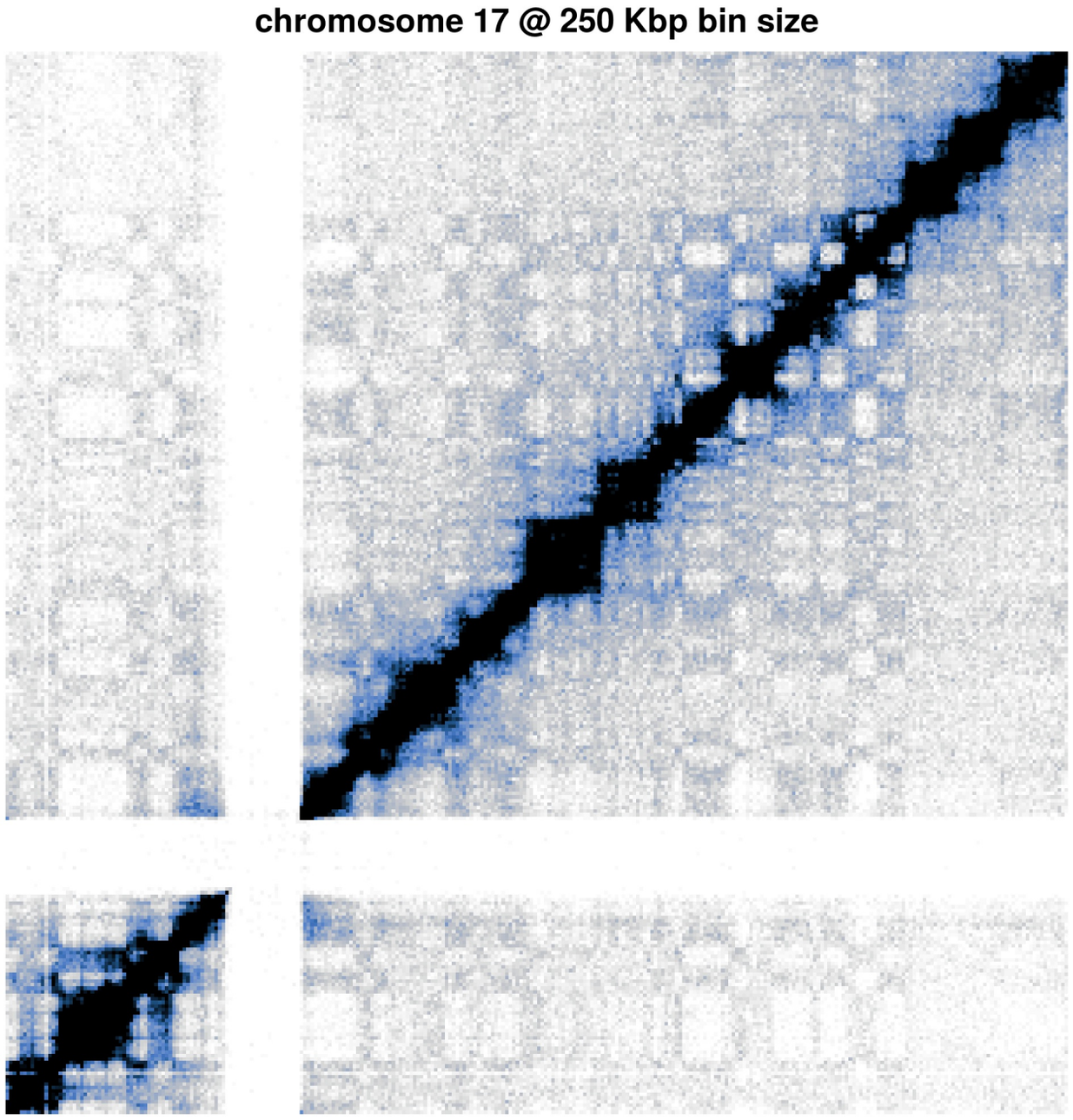
♡ Suitable aberrant karyotypes

♡ As good as existing

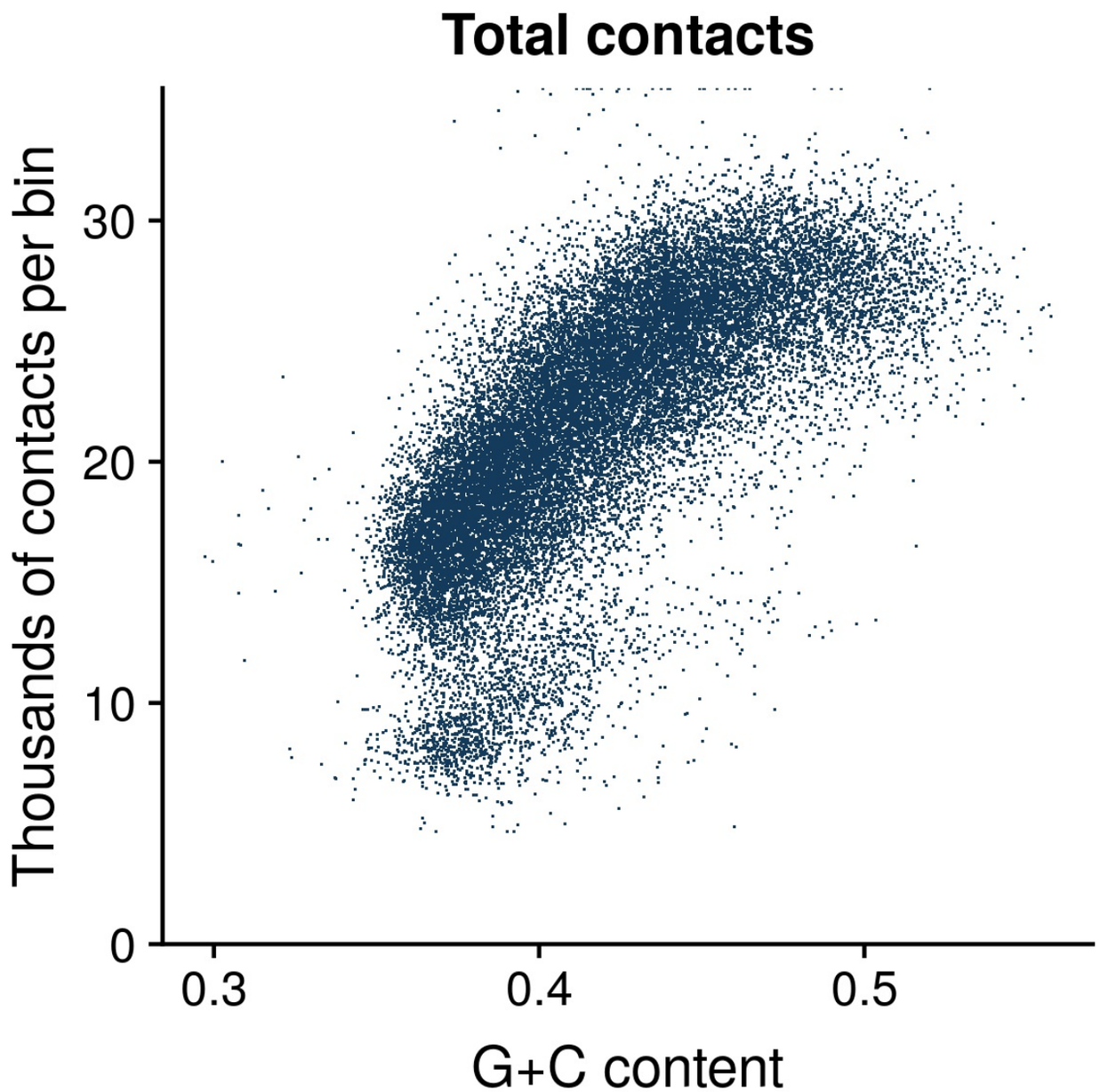
♡ Fast and scalable (high resolution)

2D → 1D

2D → 1D



2D → 1D vs. genomic features



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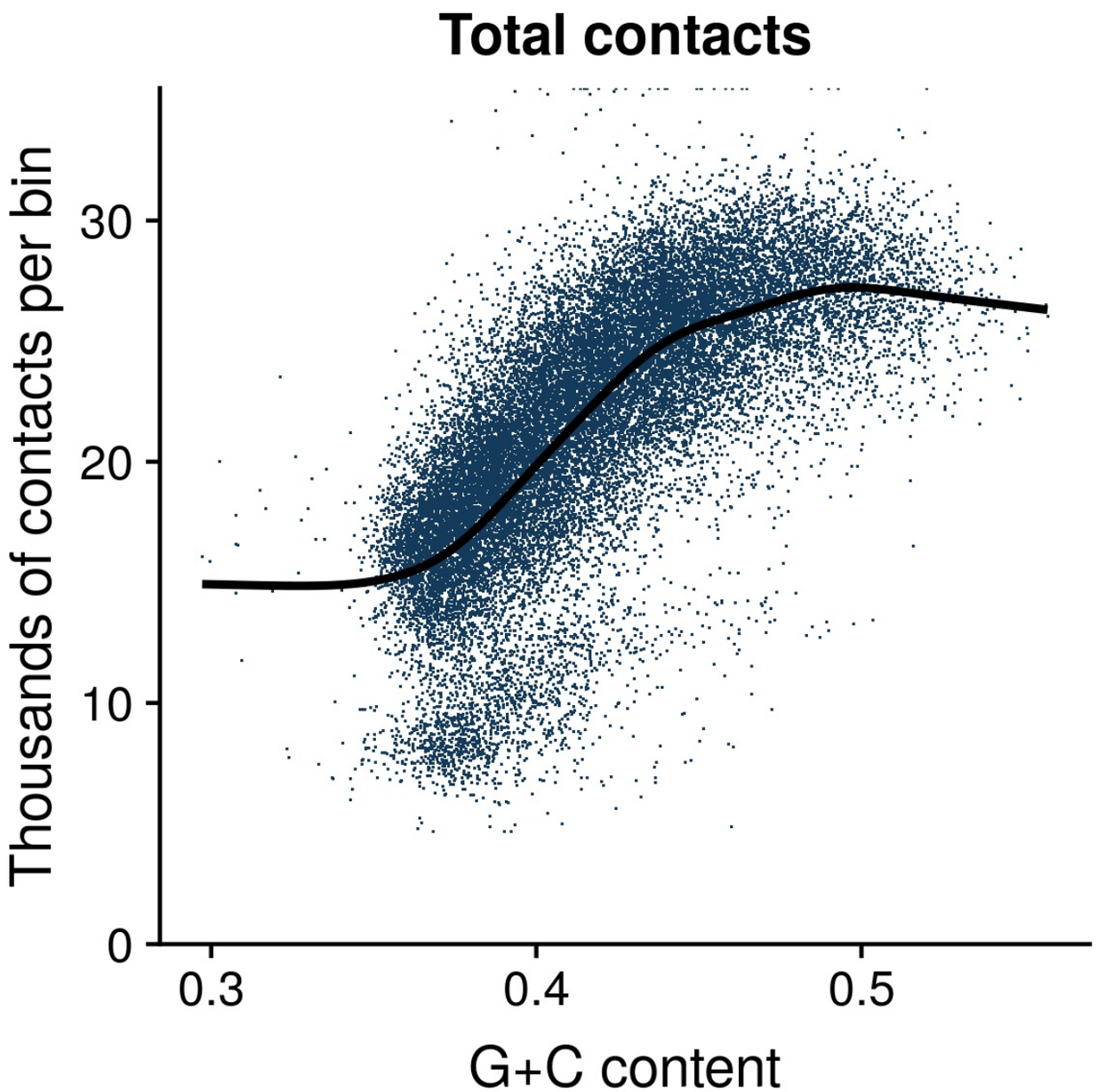
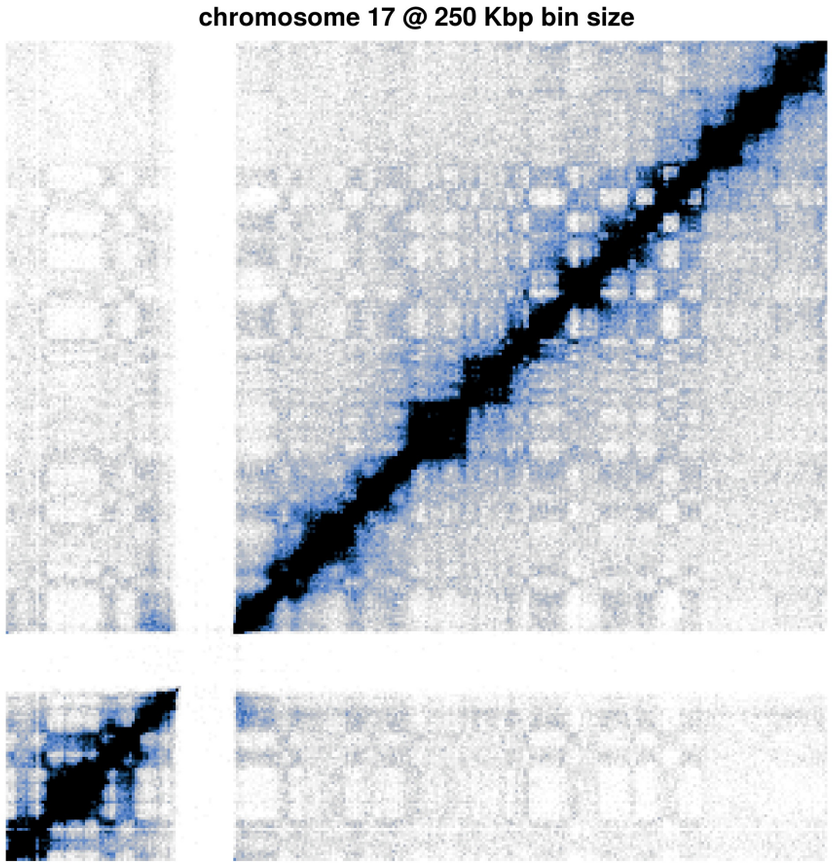


OneD model



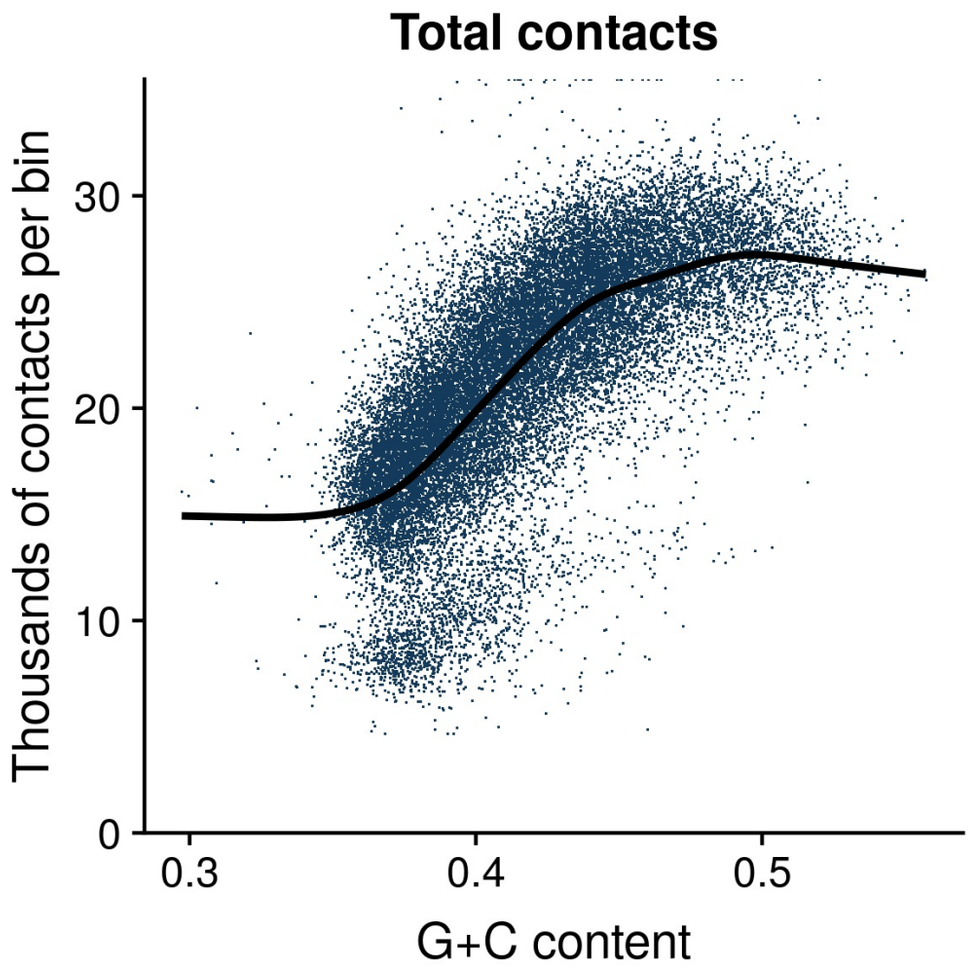
$$t_i = \sum_j^n x_{i,j} \sim NB(\lambda_i, \theta)$$

$$log\left(\lambda_i\right) \propto \sum_k f_k(x_k)$$

$$\lambda_i^{'} = \frac{\lambda_i}{\sum_i^n \lambda_j / n}$$

$$\hat{x}_{i,j} = \frac{x_{i,j}}{\sqrt{\lambda_i^{'} \lambda_j^{'}}}$$

OneD model



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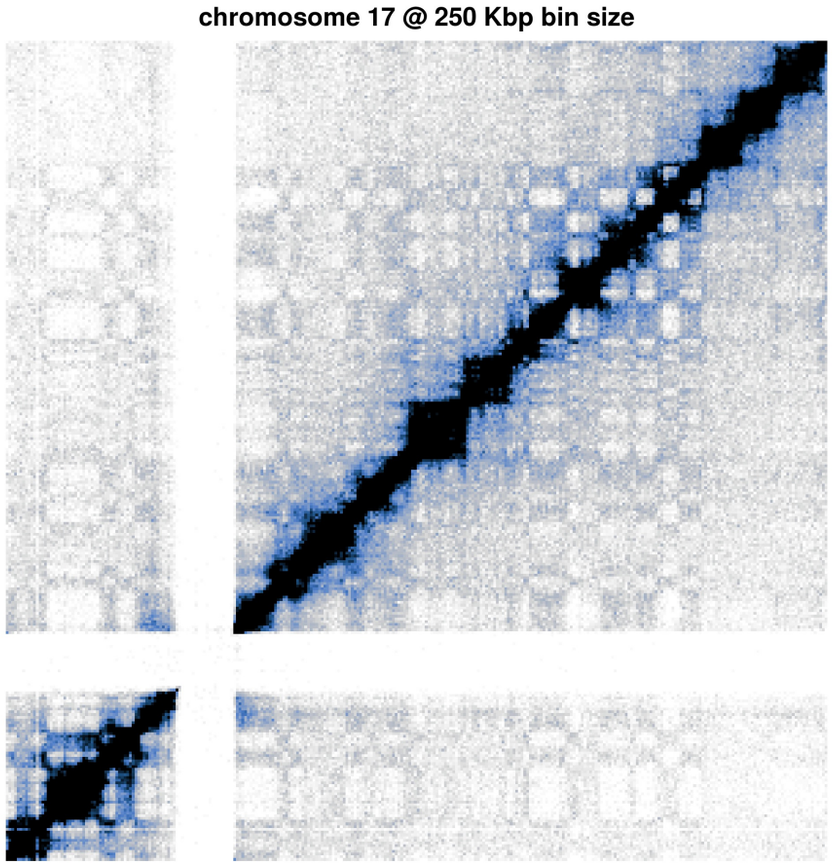
OneD model



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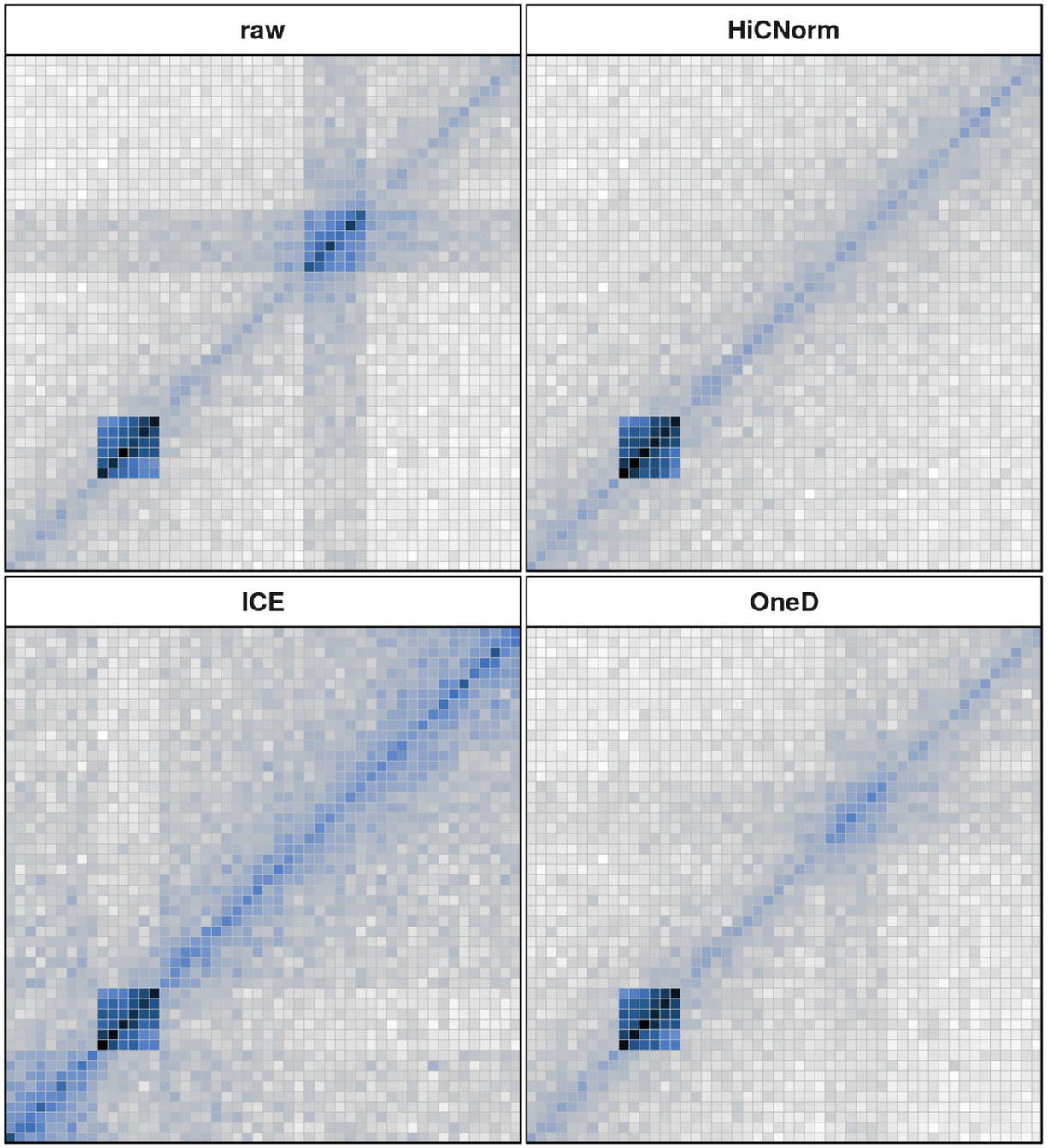
OneD in action



OneD performance

Benchmark strategy

Compare methods

Previous, **OneD** and doing nothing (raw)

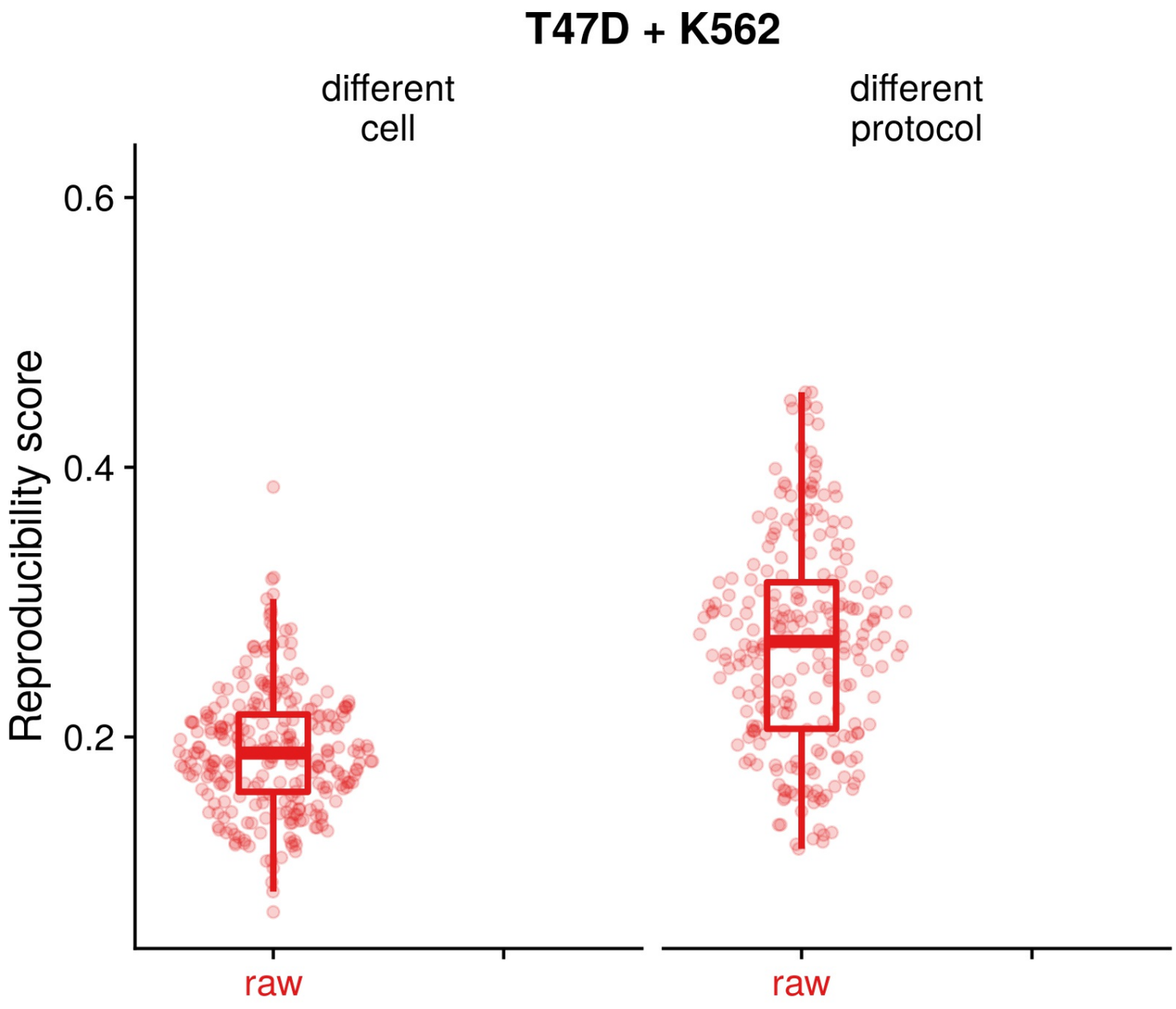
Undesired variability

Different protocols (restriction enzyme, in-situ / diluted, lab, etc ...)

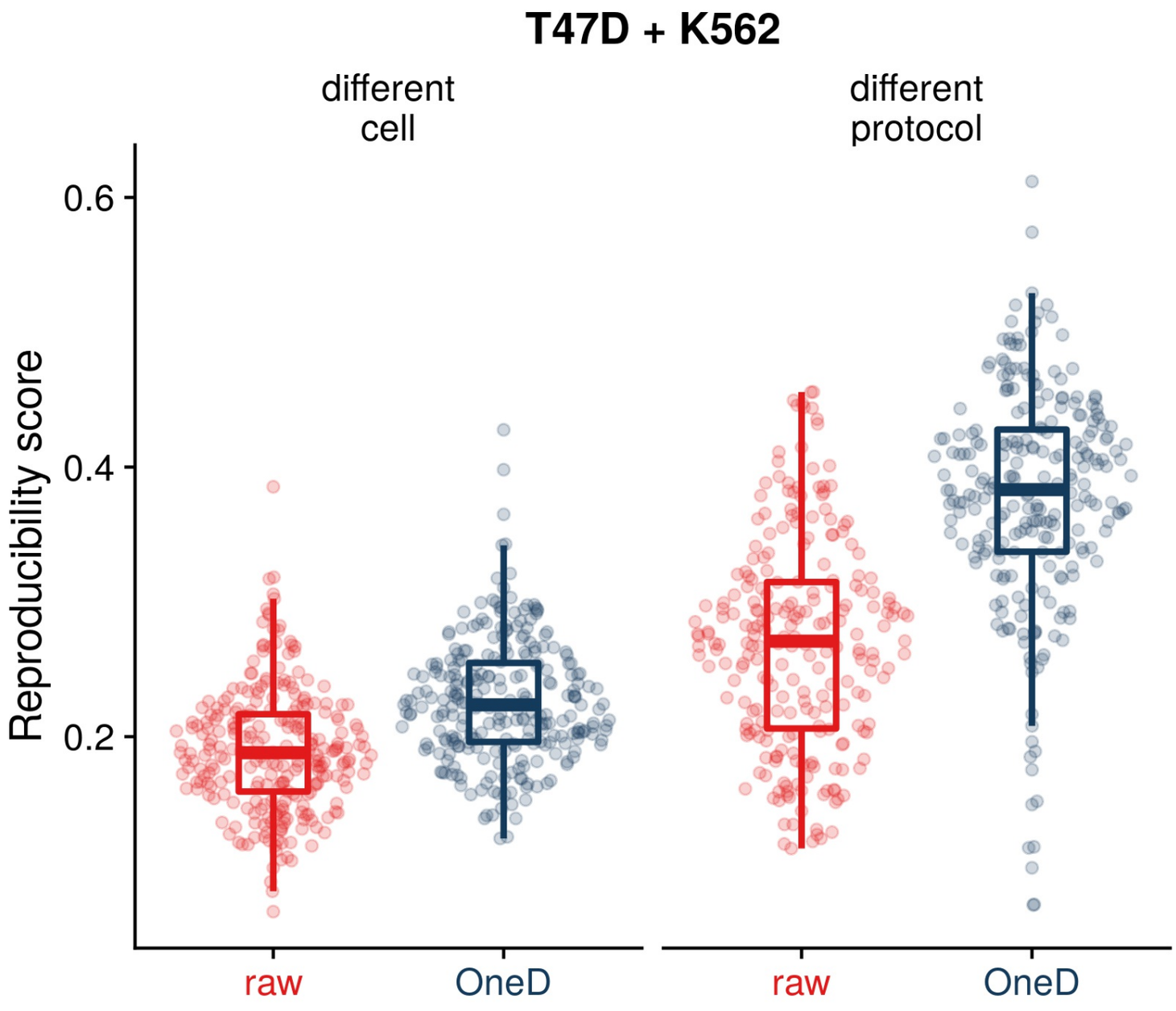
Relevant variability

Different cell types

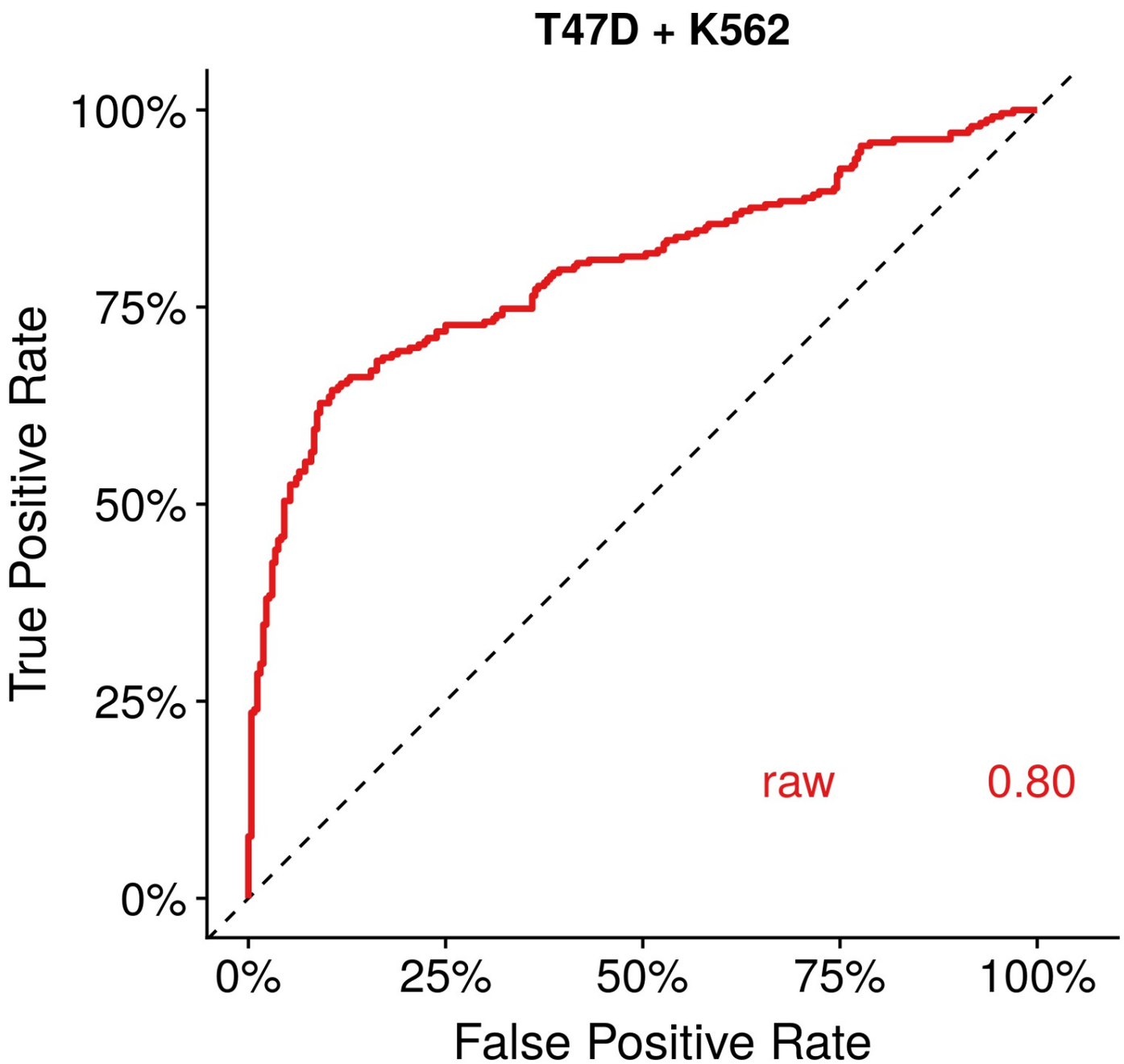
Pair-wise comparison



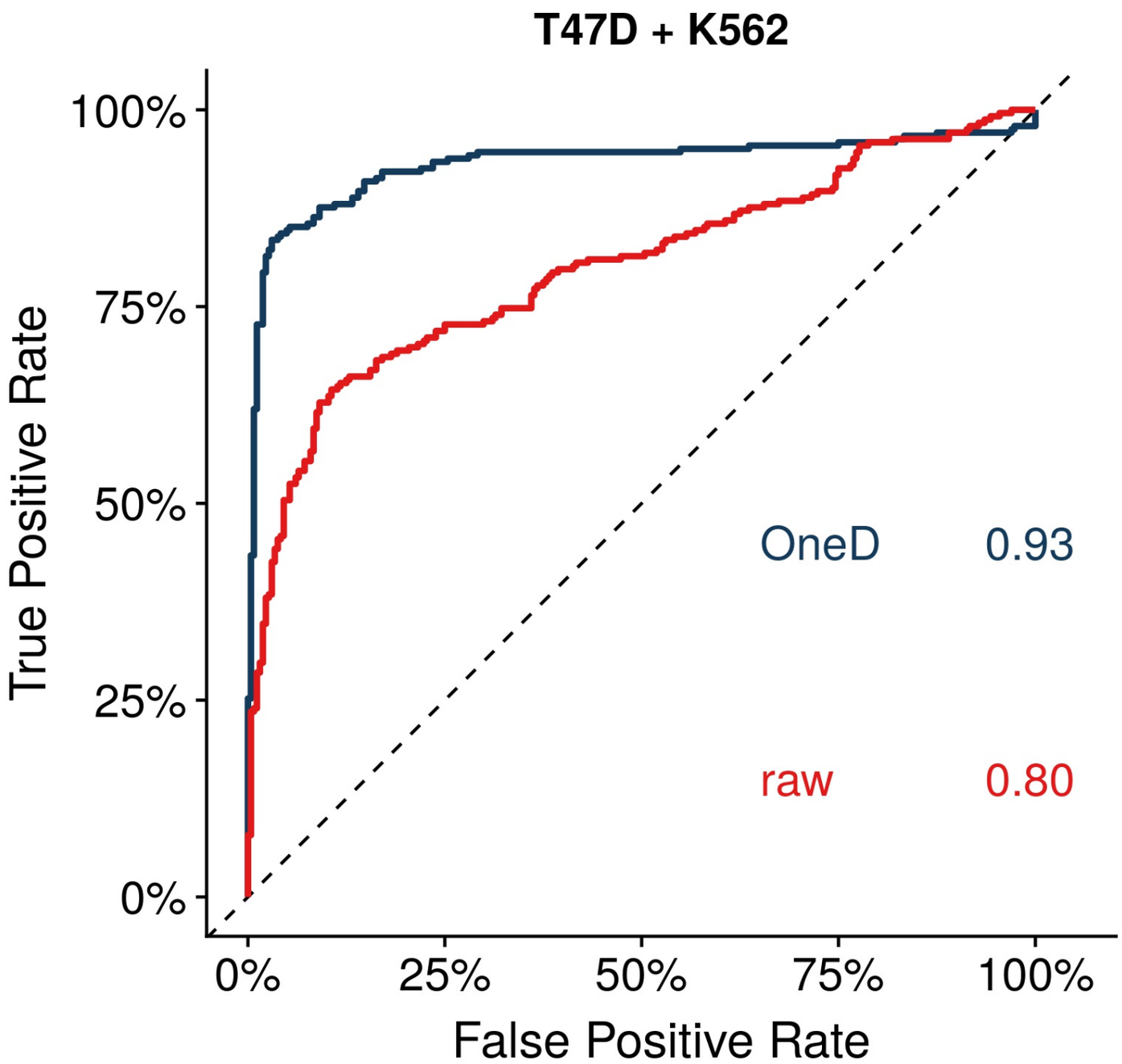
Pair-wise comparison



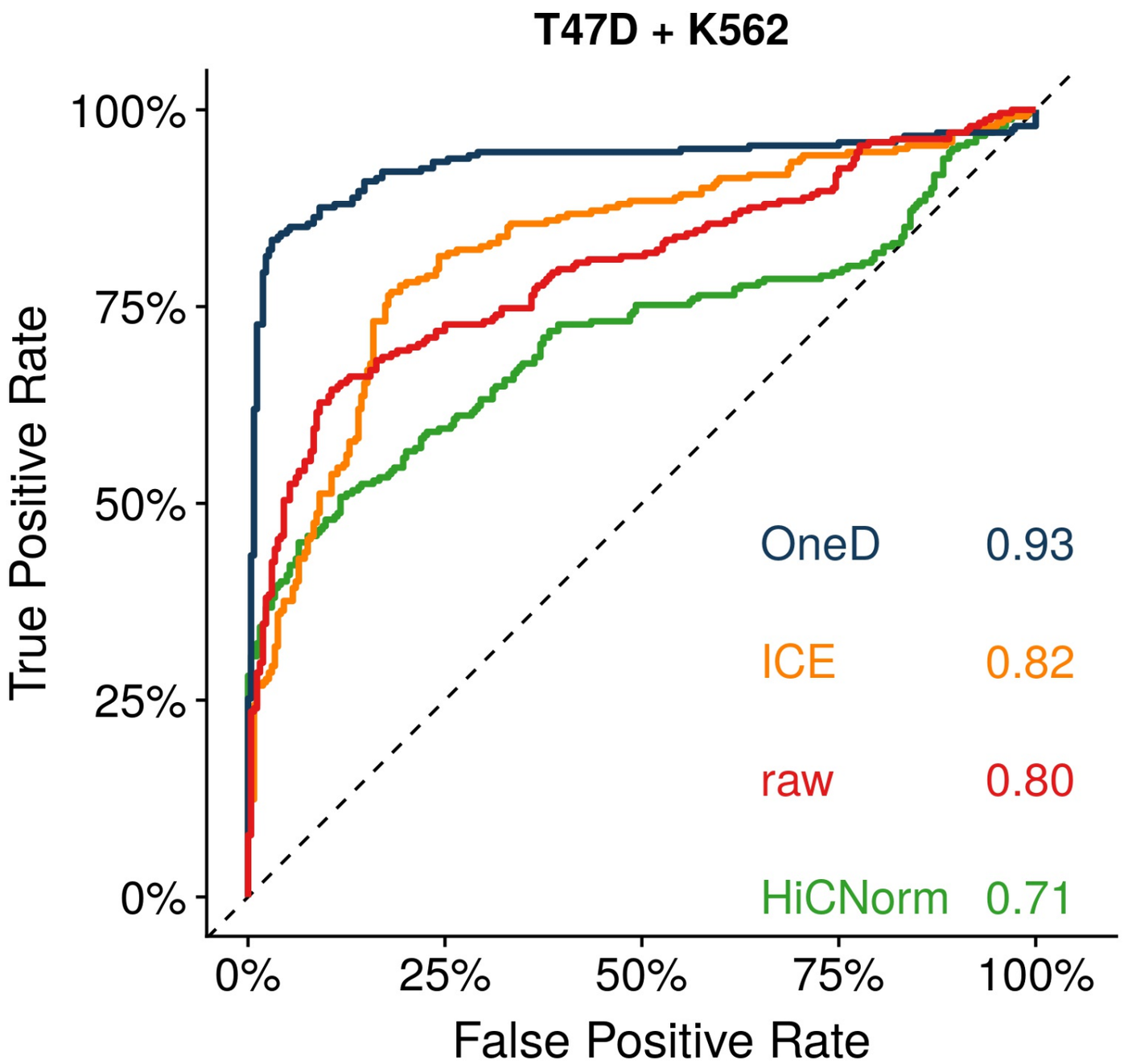
ROC and AUC


T47D + K562
100%
75%
50%
25%
0%
True Positive Rate
0%
25%
50%
75%
100%
False Positive Rate
raw
0.80

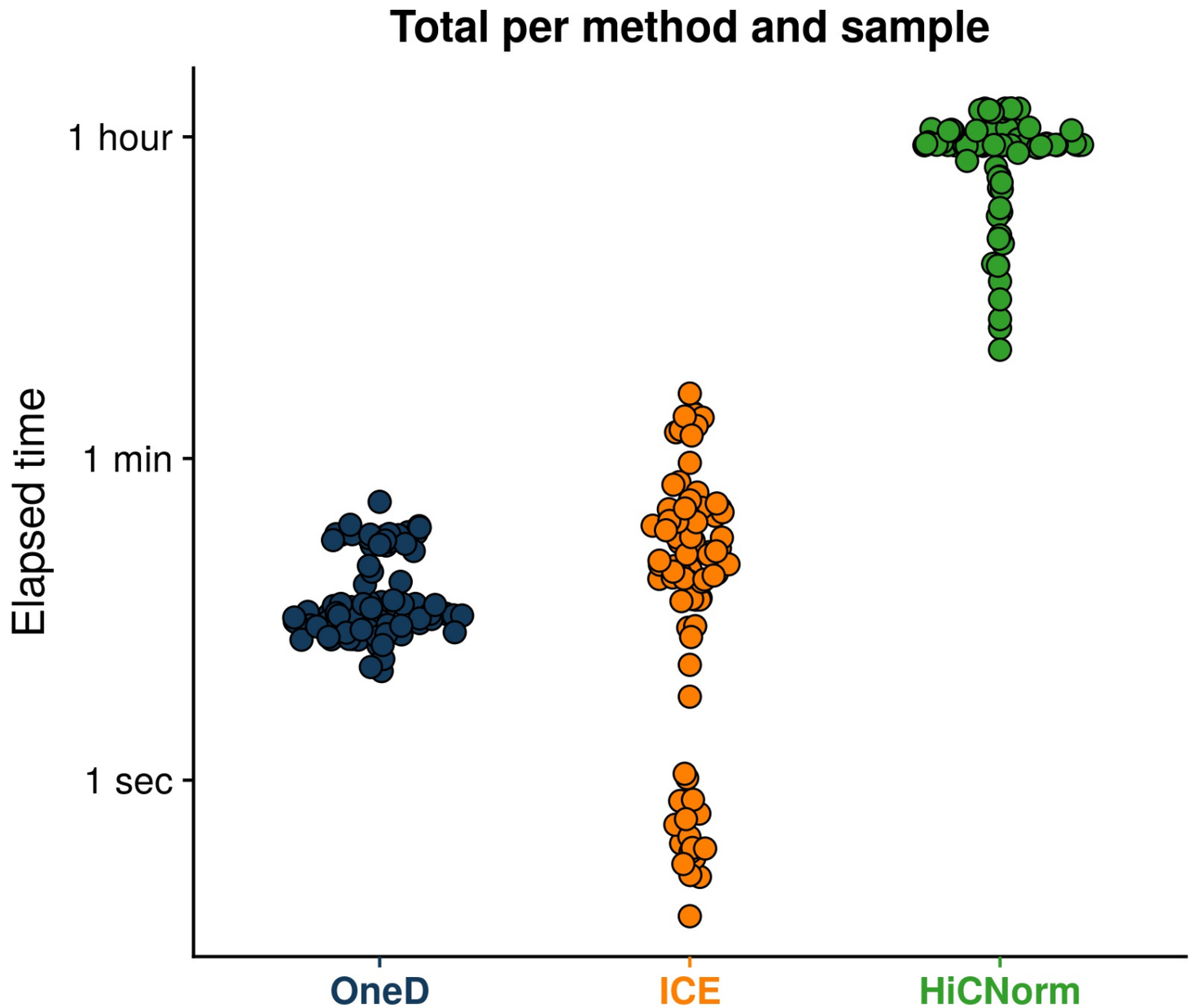
ROC and AUC


T47D + K562
100%
75%
50%
25%
0%
True Positive Rate
0%
25%
50%
75%
100%
False Positive Rate
OneD 0.93
raw 0.80

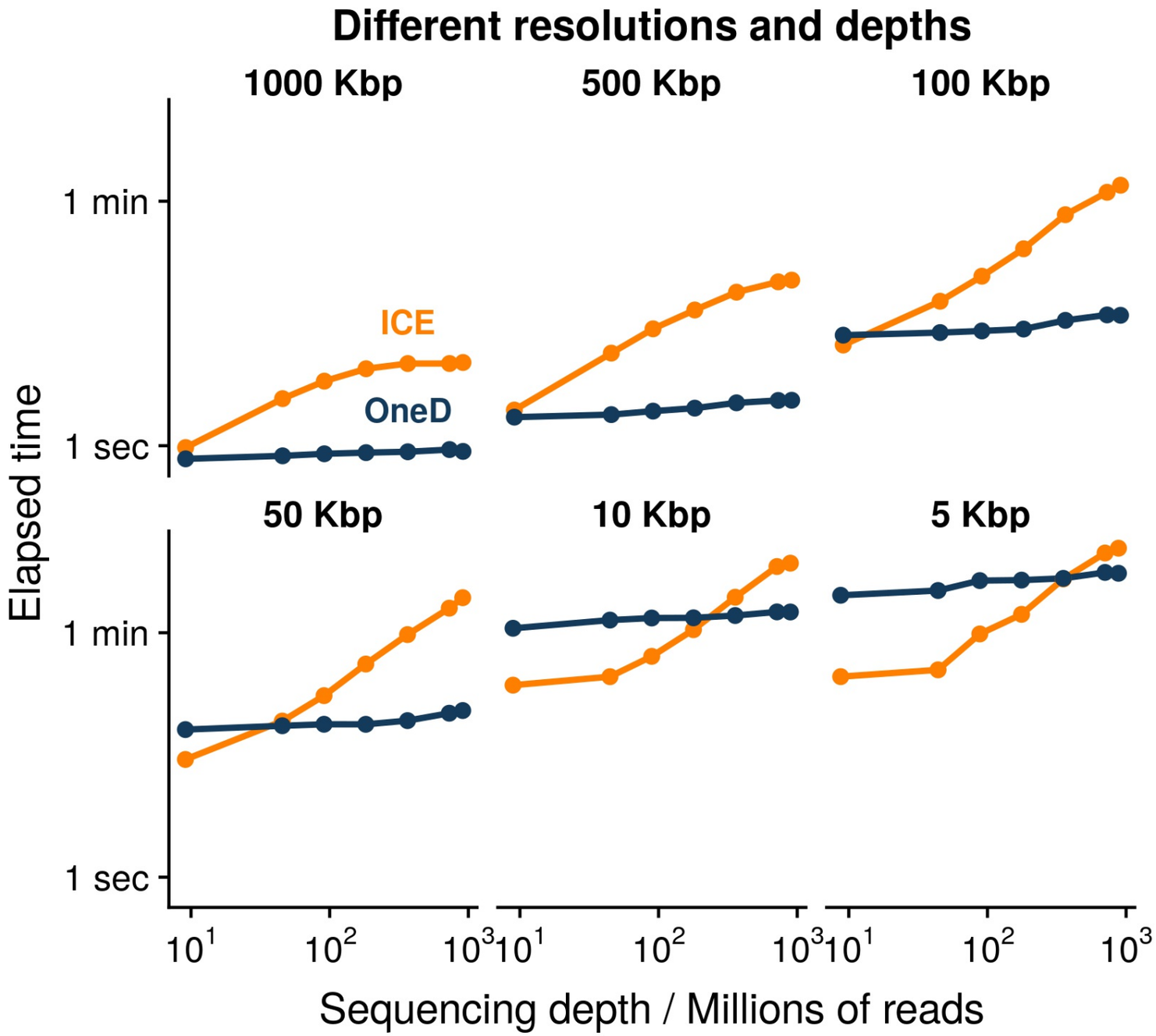
ROC and AUC


T47D + K562
100%
75%
50%
25%
0%
True Positive Rate
0%
25%
50%
75%
100%
False Positive Rate
OneD 0.93
ICE 0.82
raw 0.80
HiCNorm 0.71

Speed and resolution



Speed and resolution



Wish list

♡ Suitable aberrant karyotypes ✓

♡ ~~As good as~~ Better than existing ✓

♡ Fast and scalable (high resolution) ✓

OneD availability

R package

https://github.com/qenvio/dryhic

Paper

Vidal, E. et al. (2018)

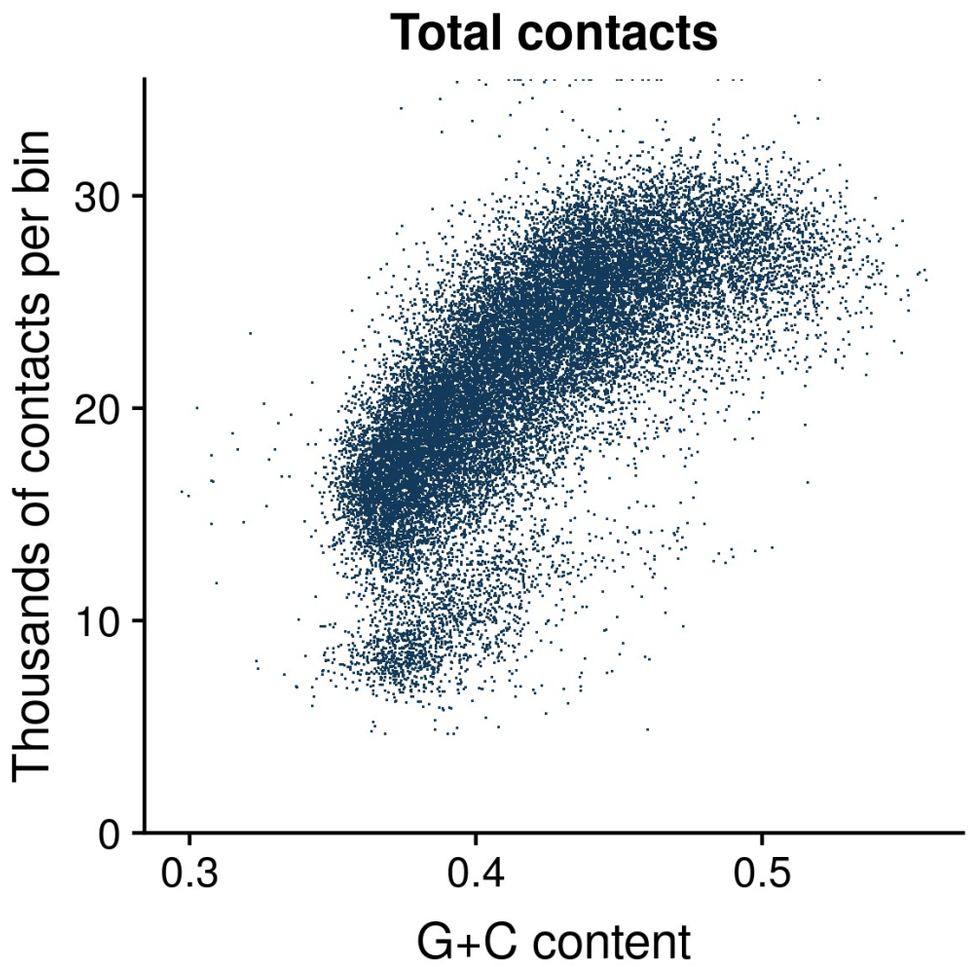
Nucleic acids research

https://doi.org/10.1093/nar/gky064

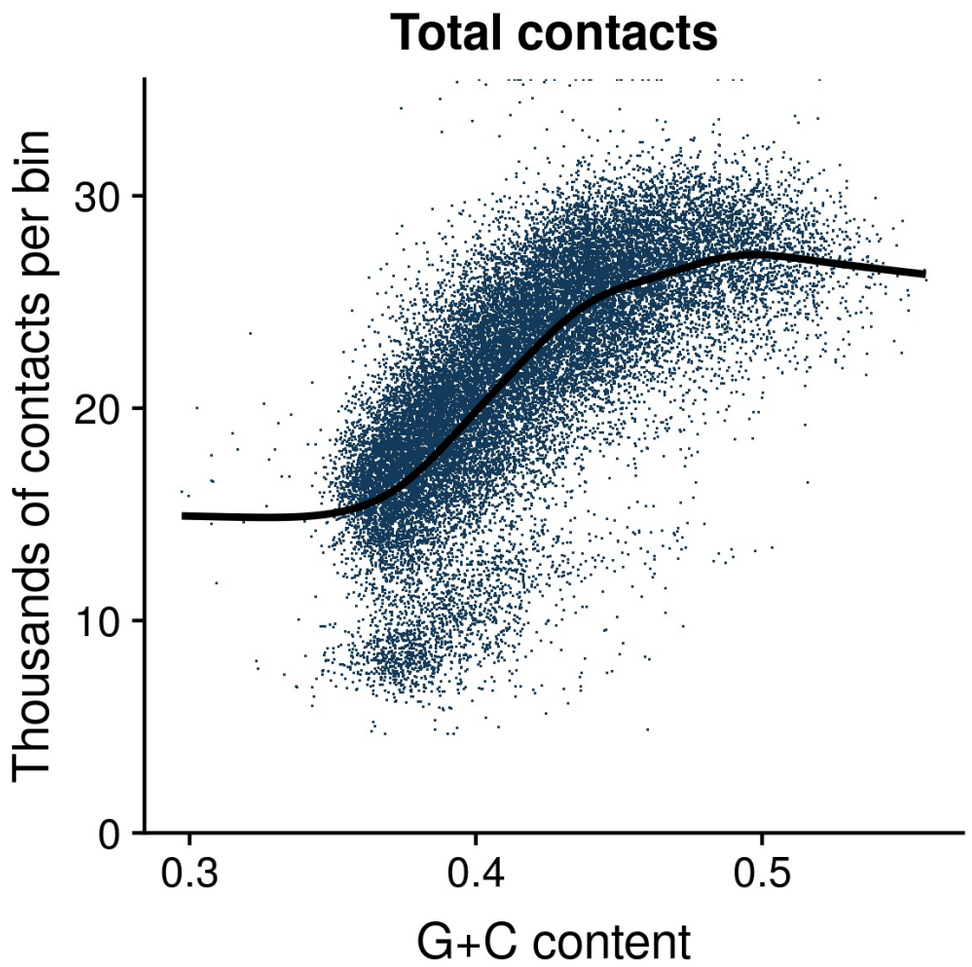
Exploiting the model

Less is more

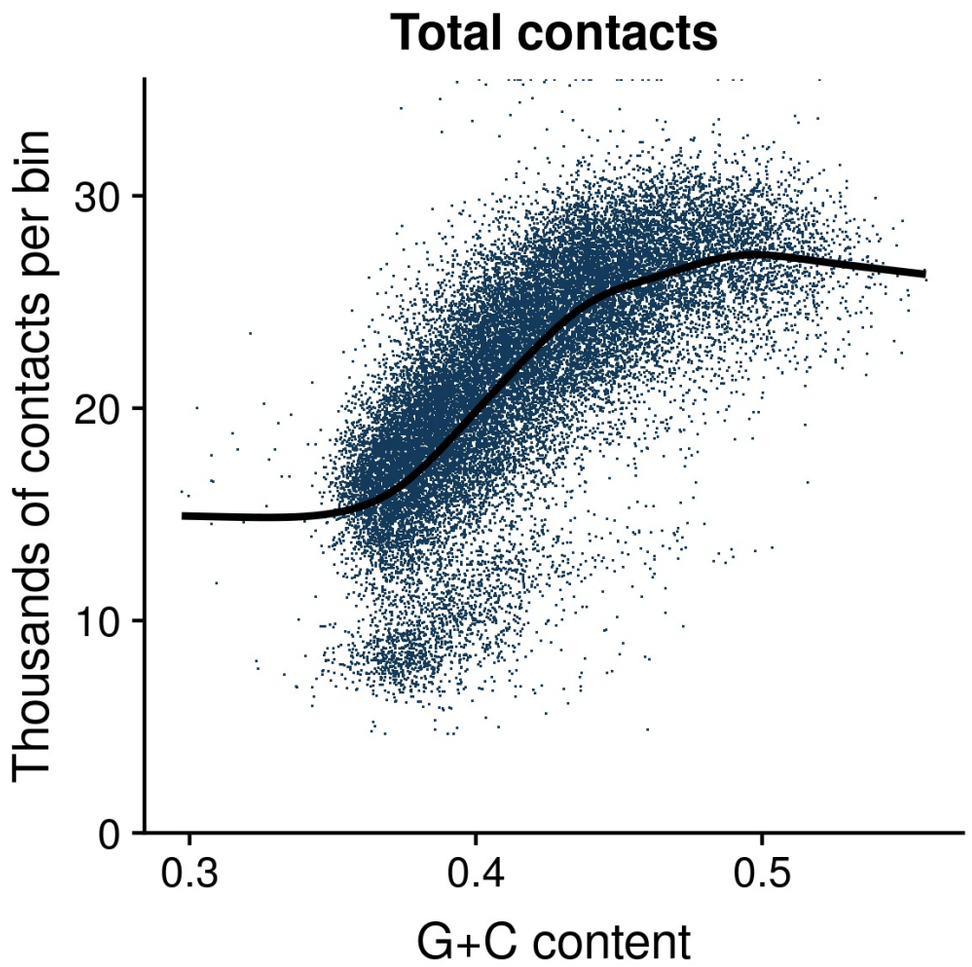
Use only a subset

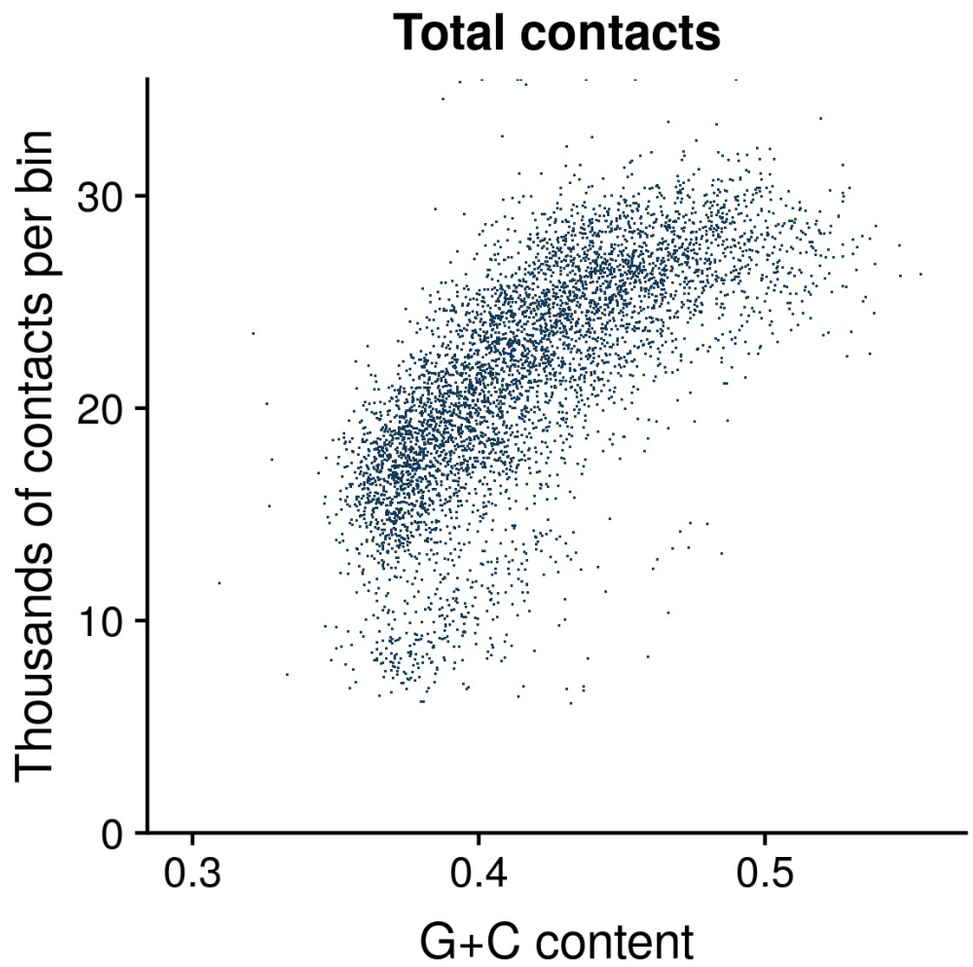


Use only a subset

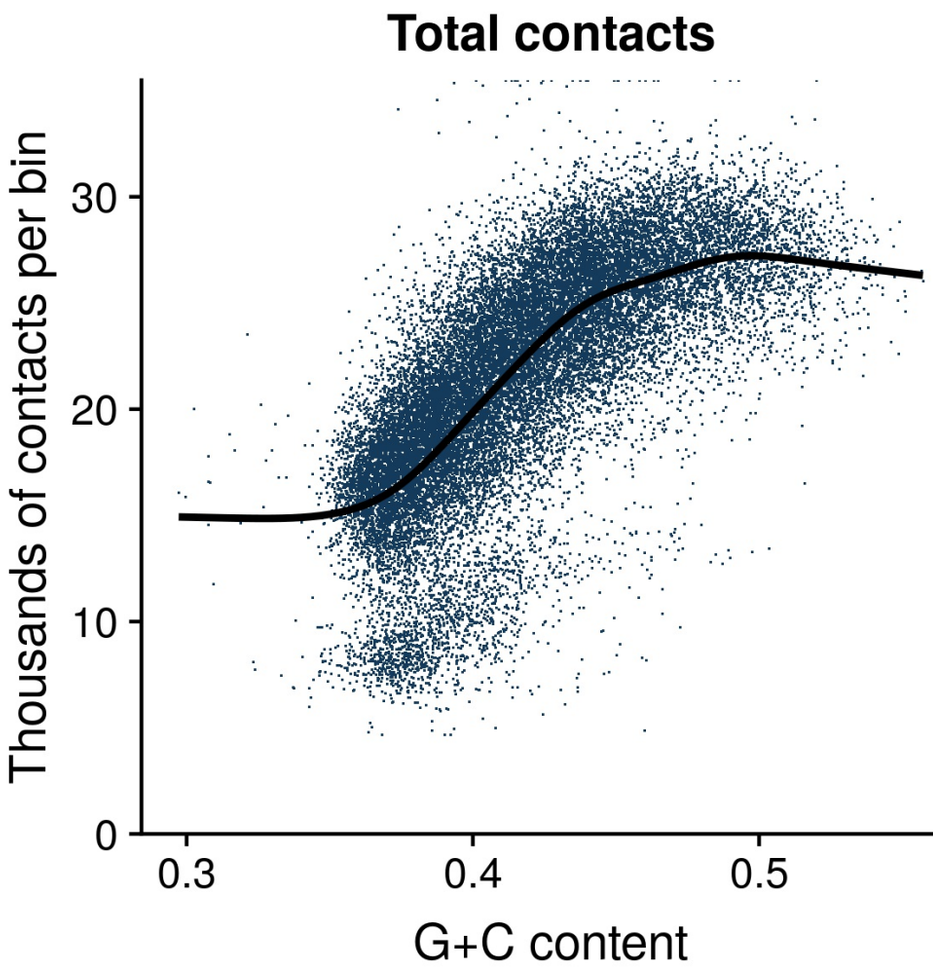


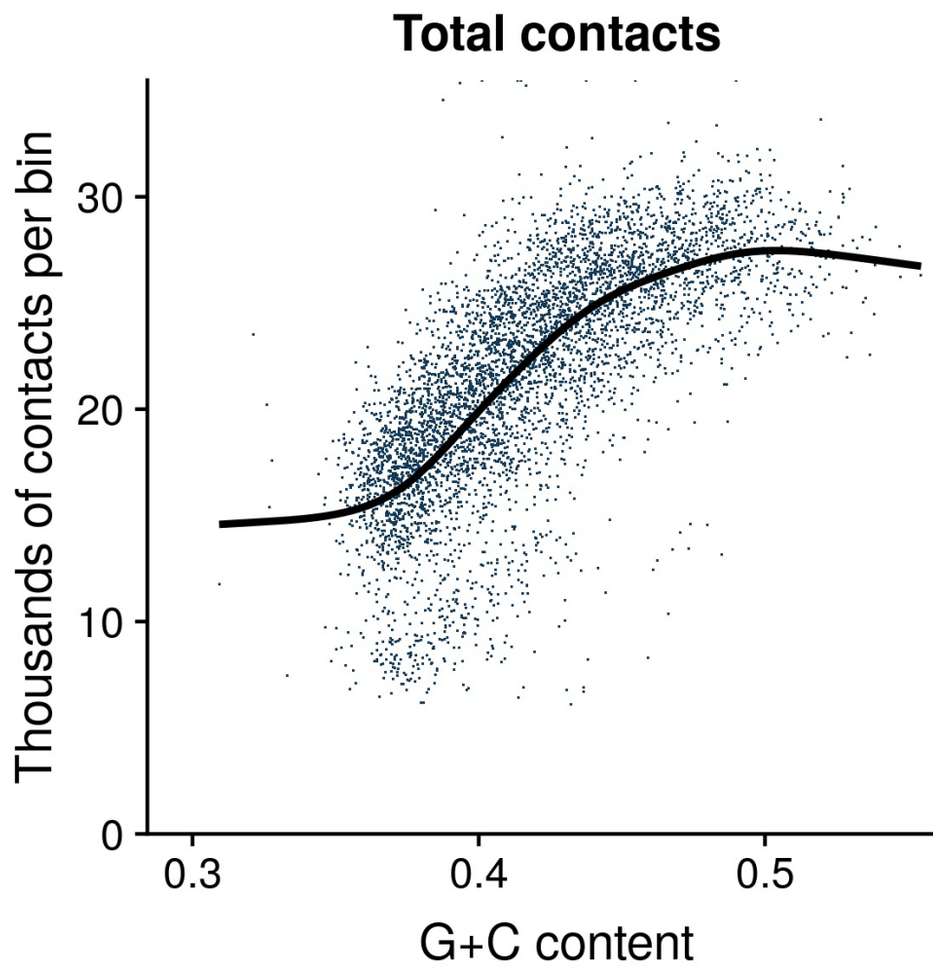
Use only a subset





Use only a subset





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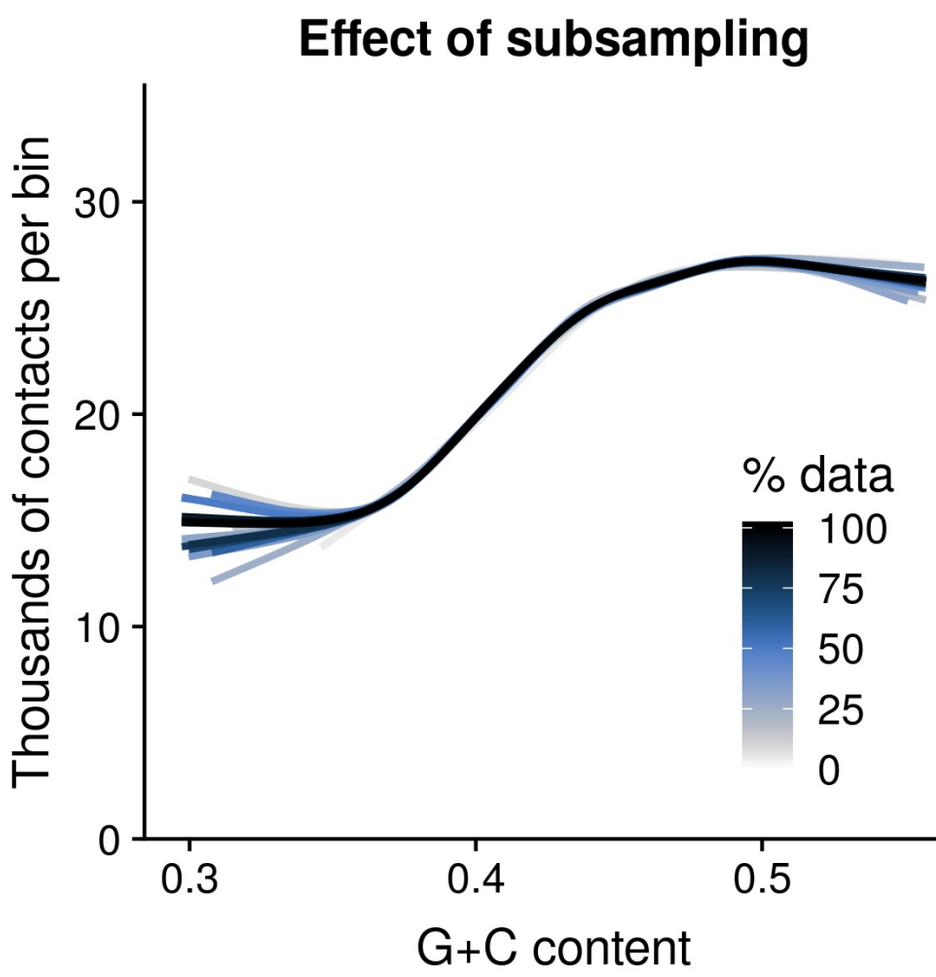
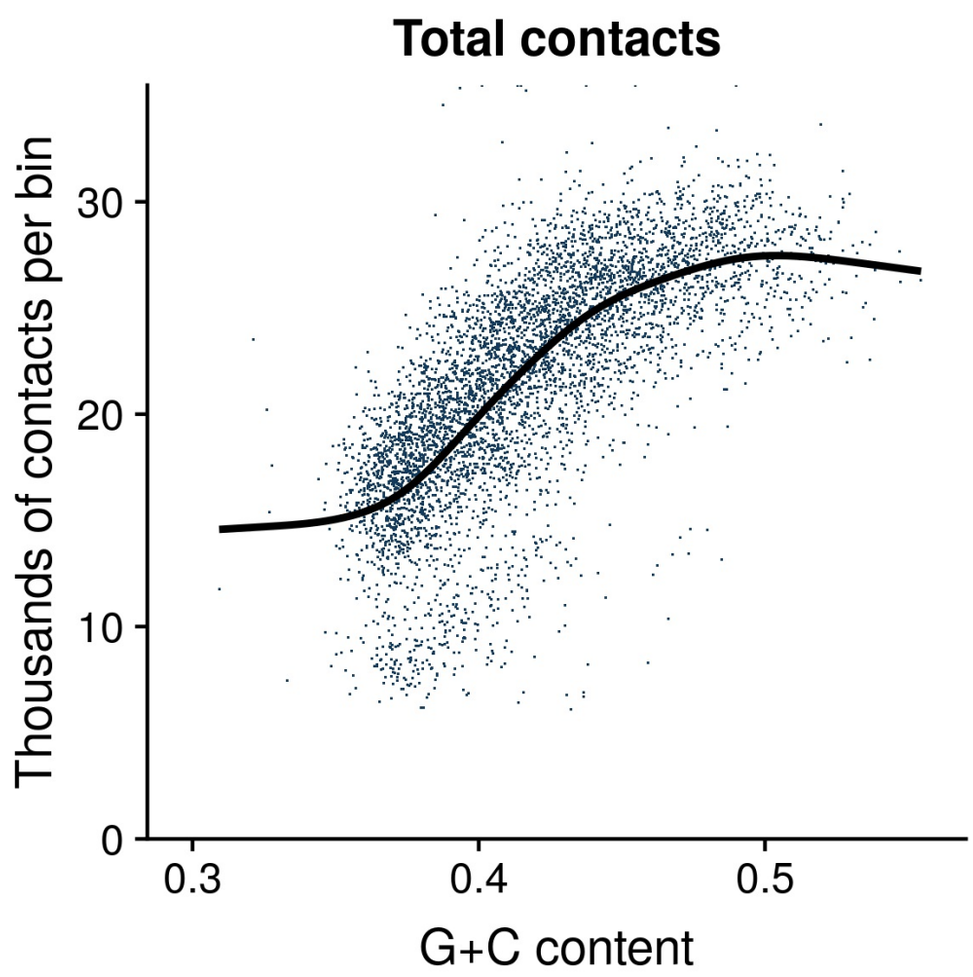
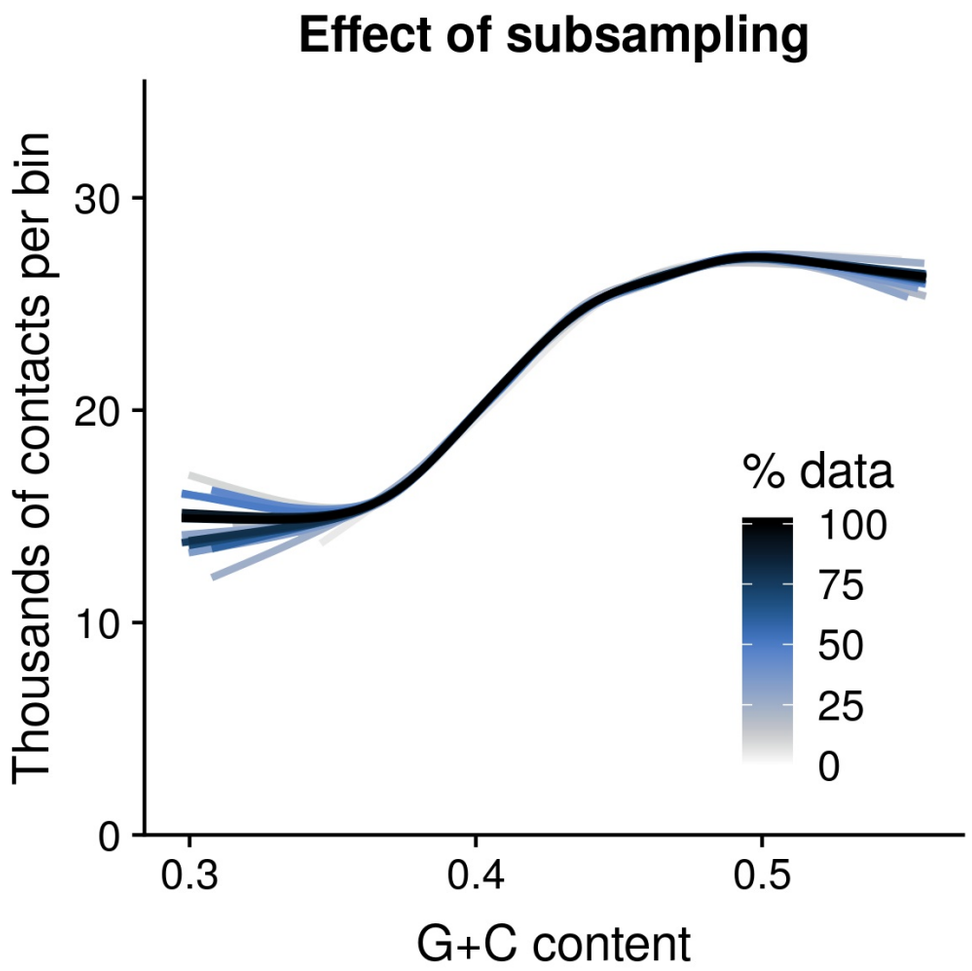
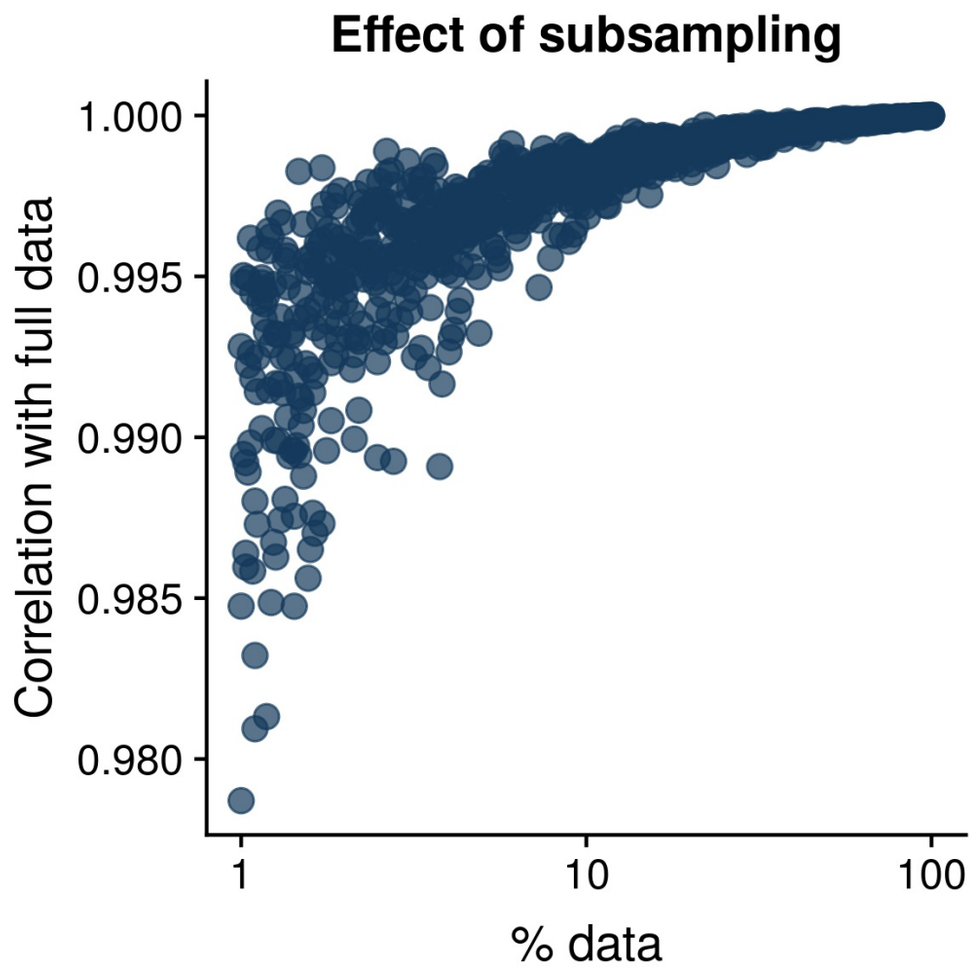




Use only a subset





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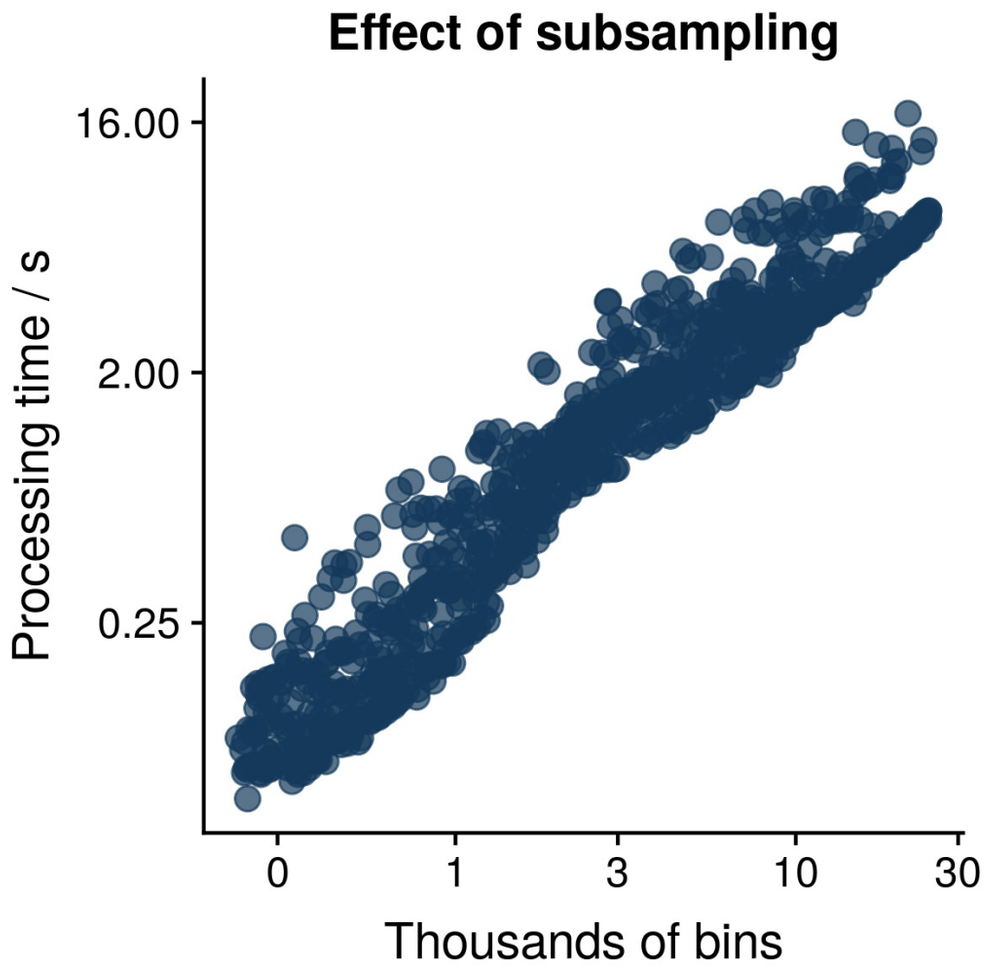

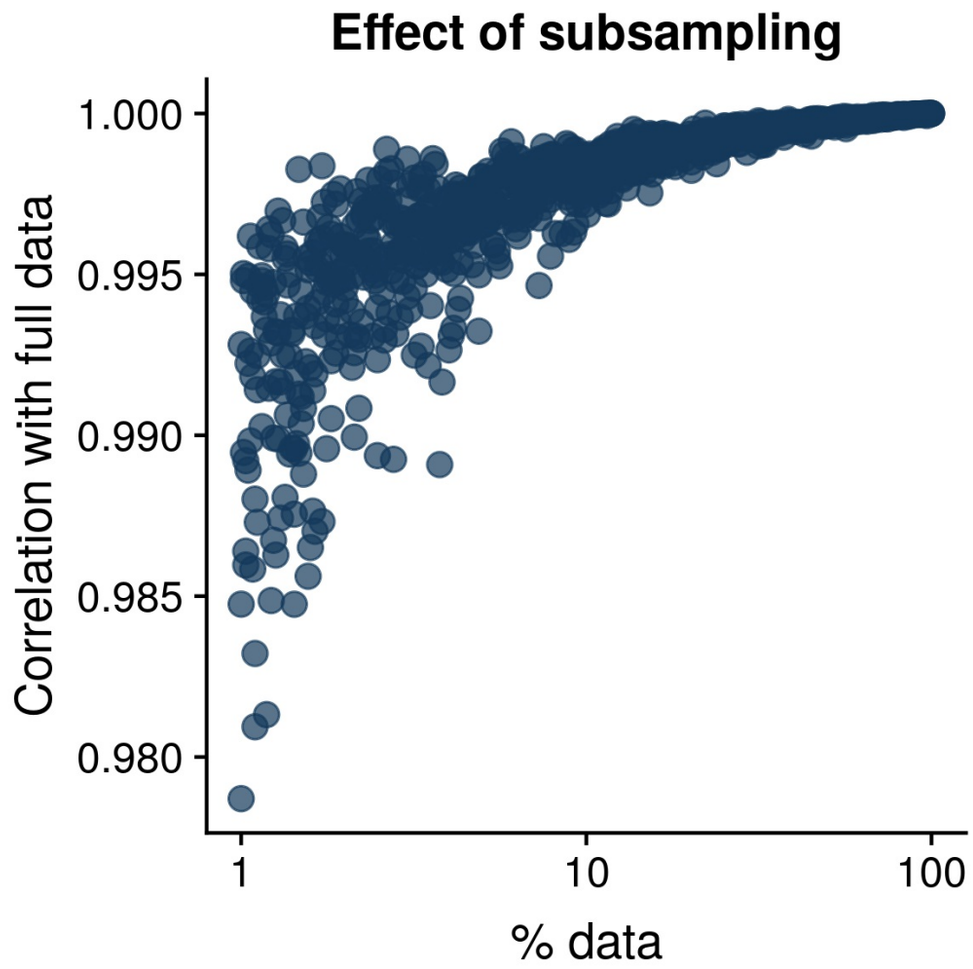

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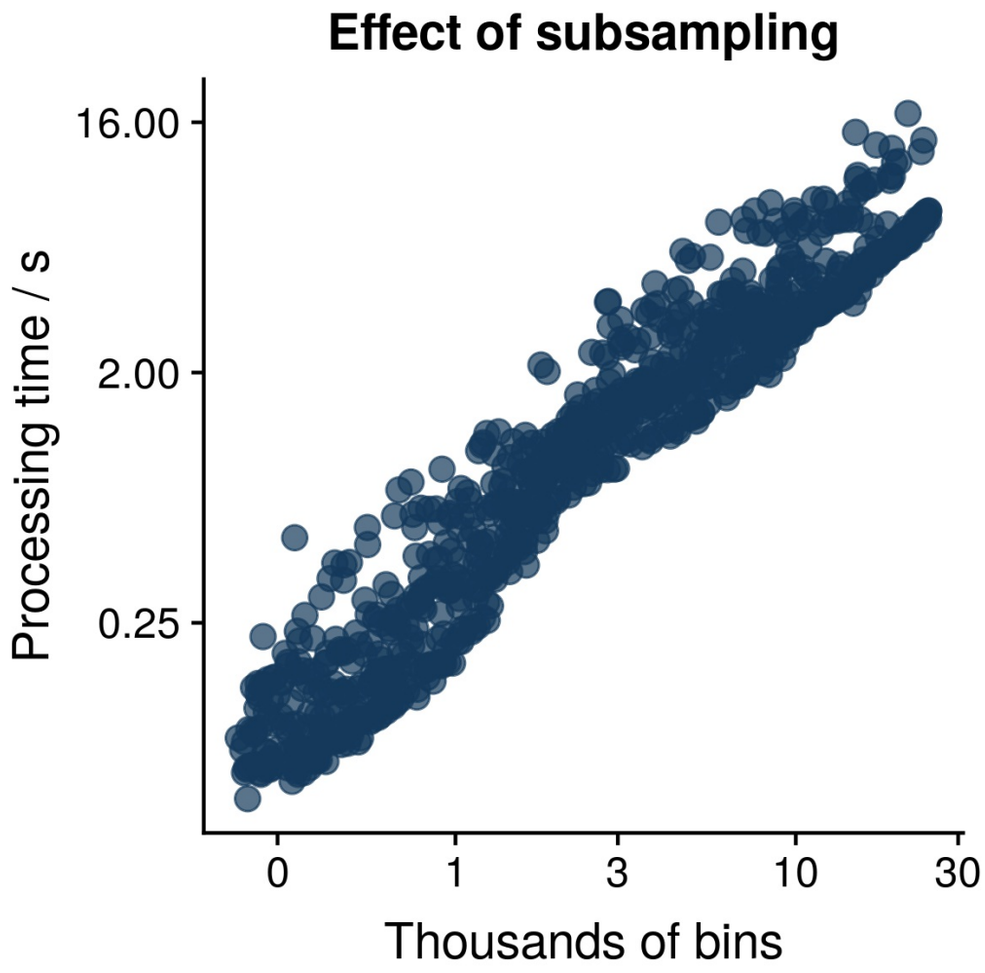
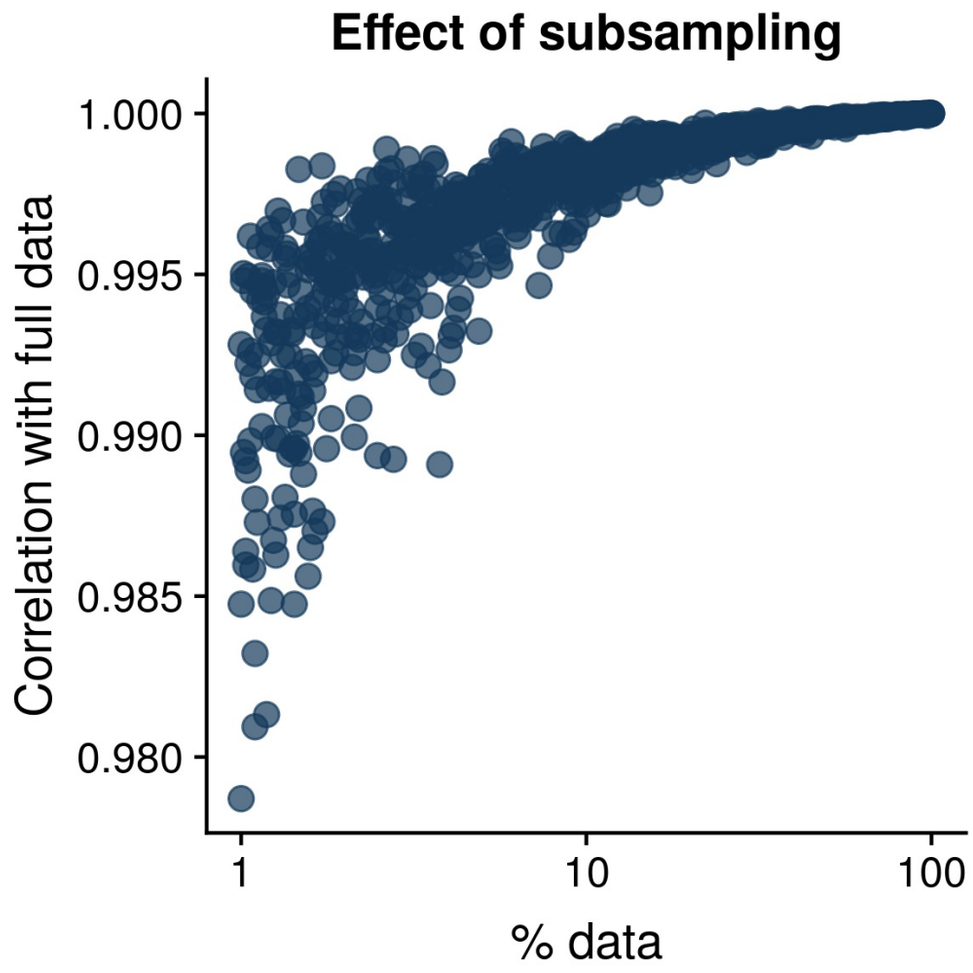


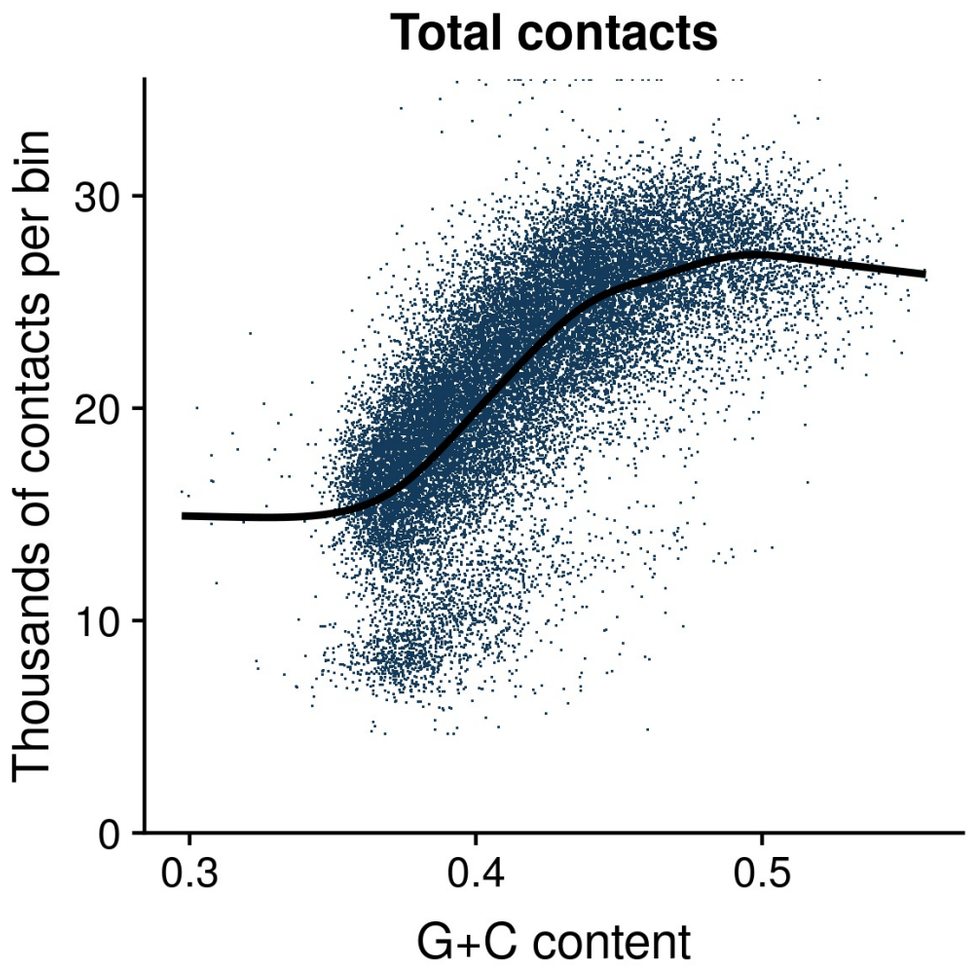


Incomplete designs ✓

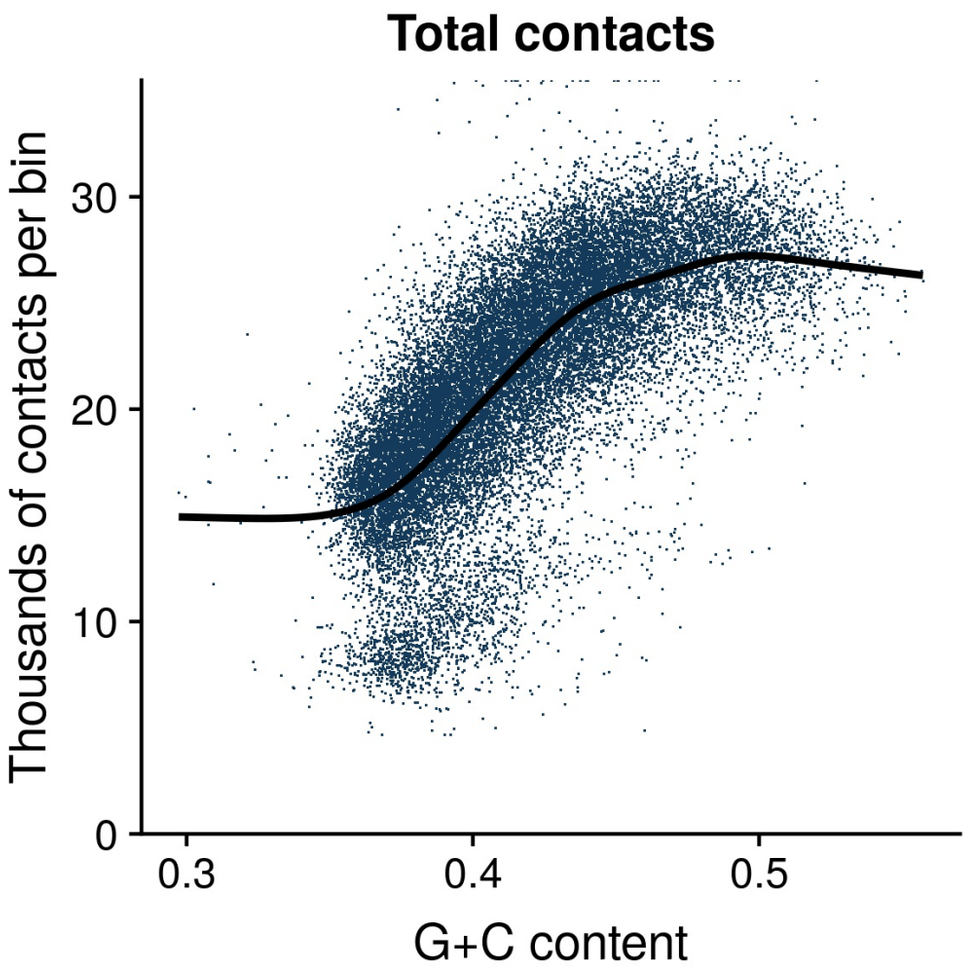
Exploiting the model

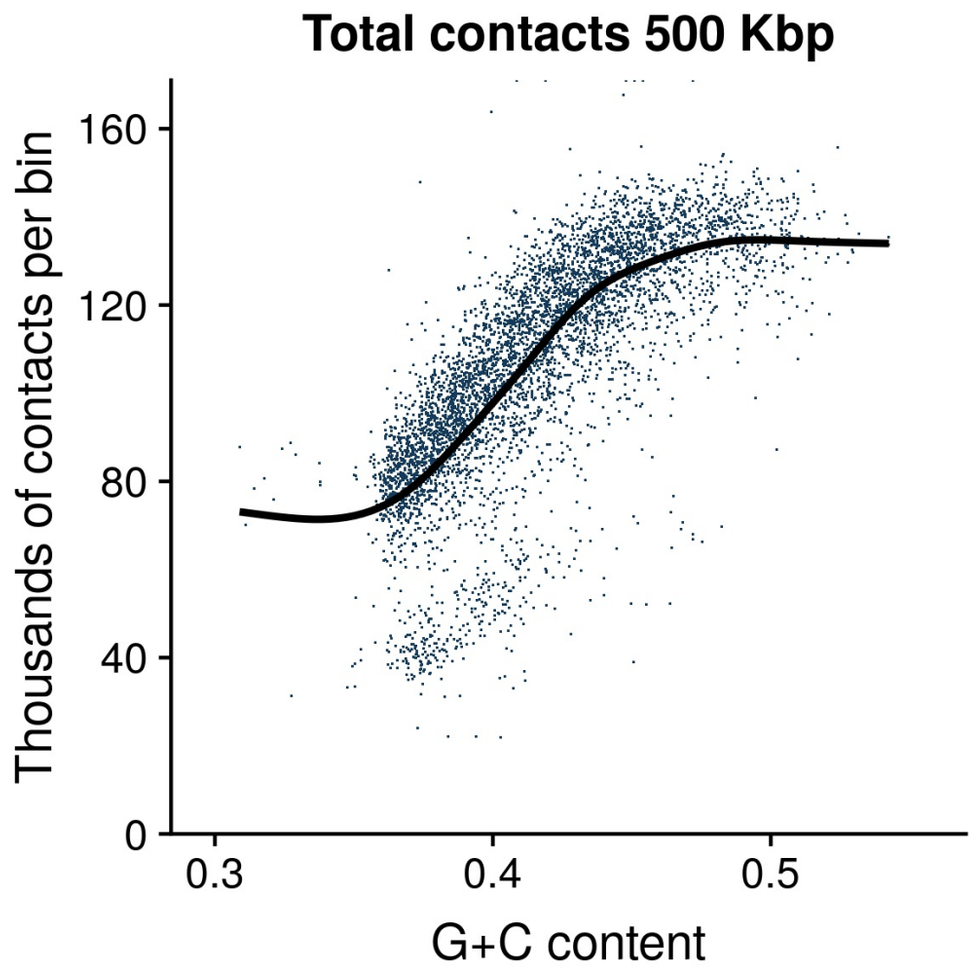
Resolution-free

Fit once, project everywhere

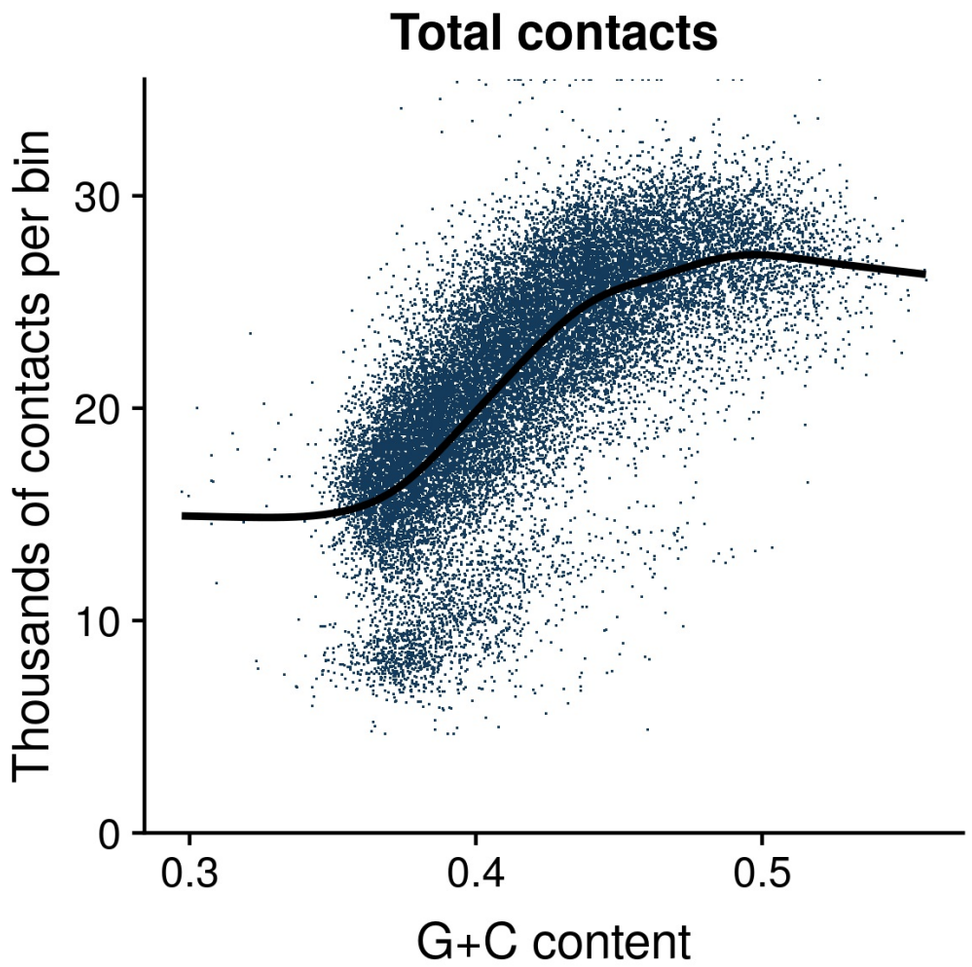


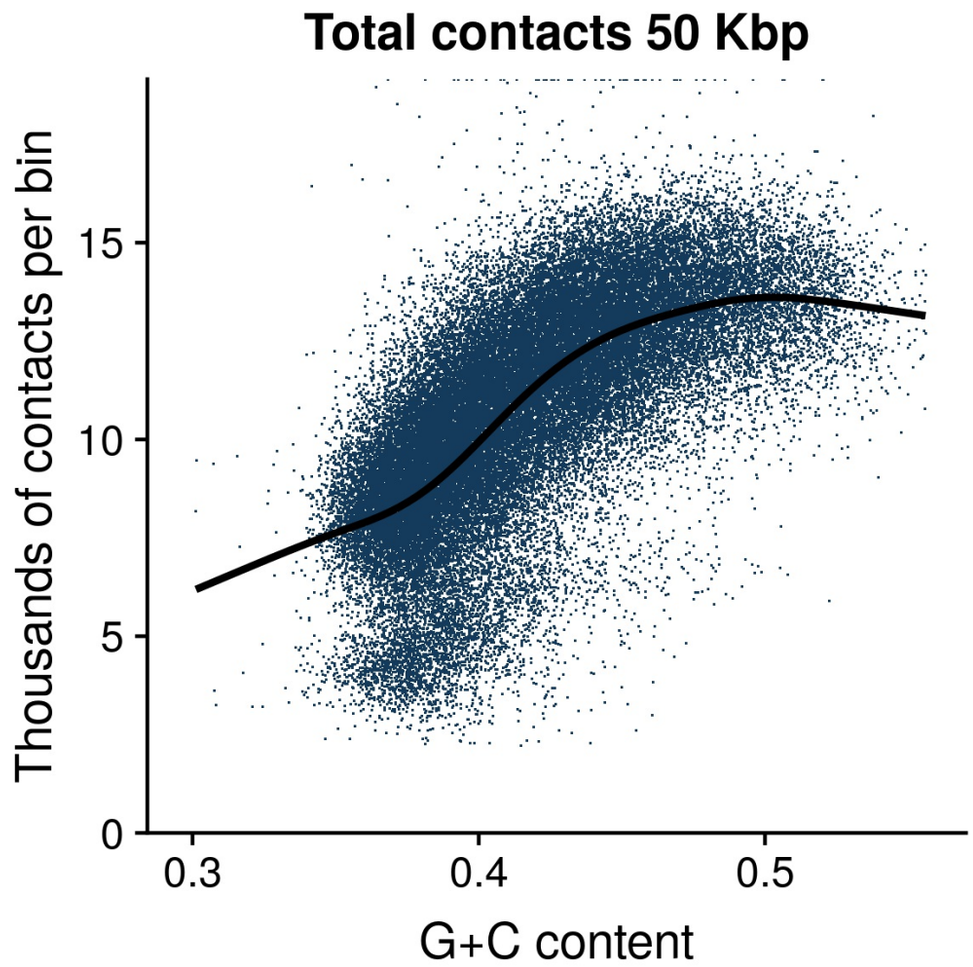
Fit once, project everywhere





Fit once, project everywhere





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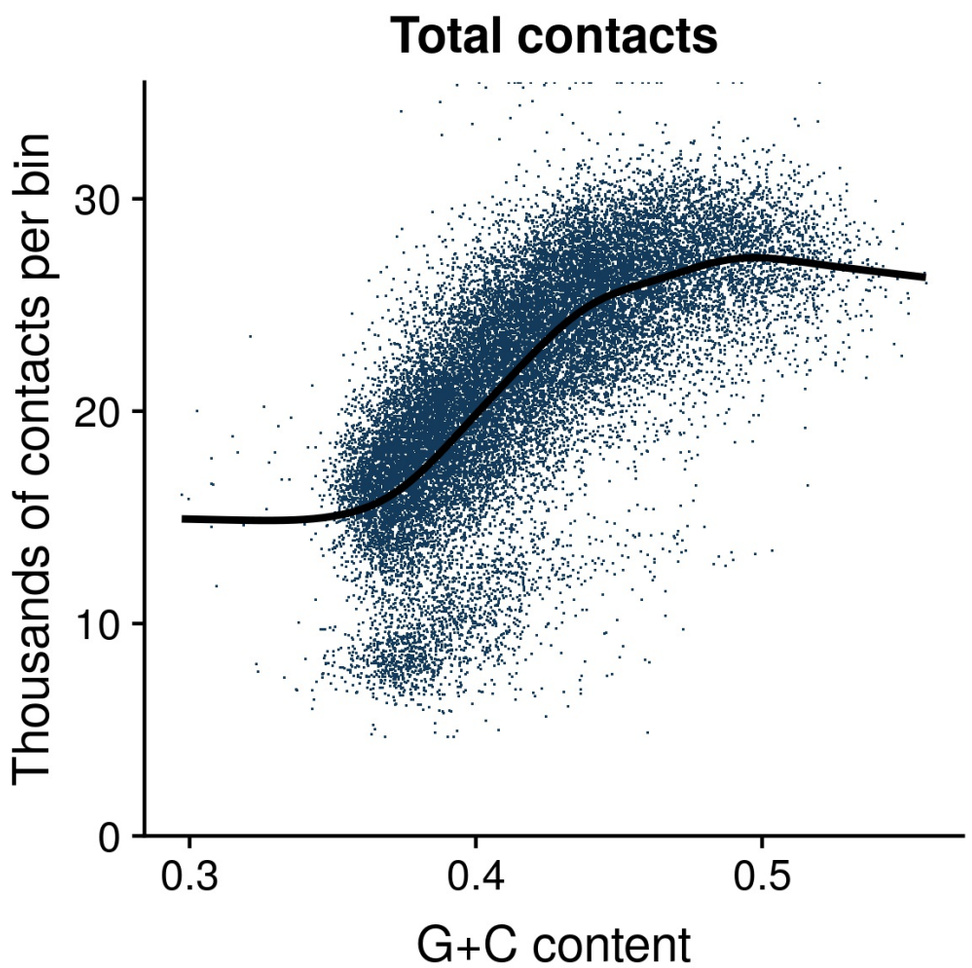
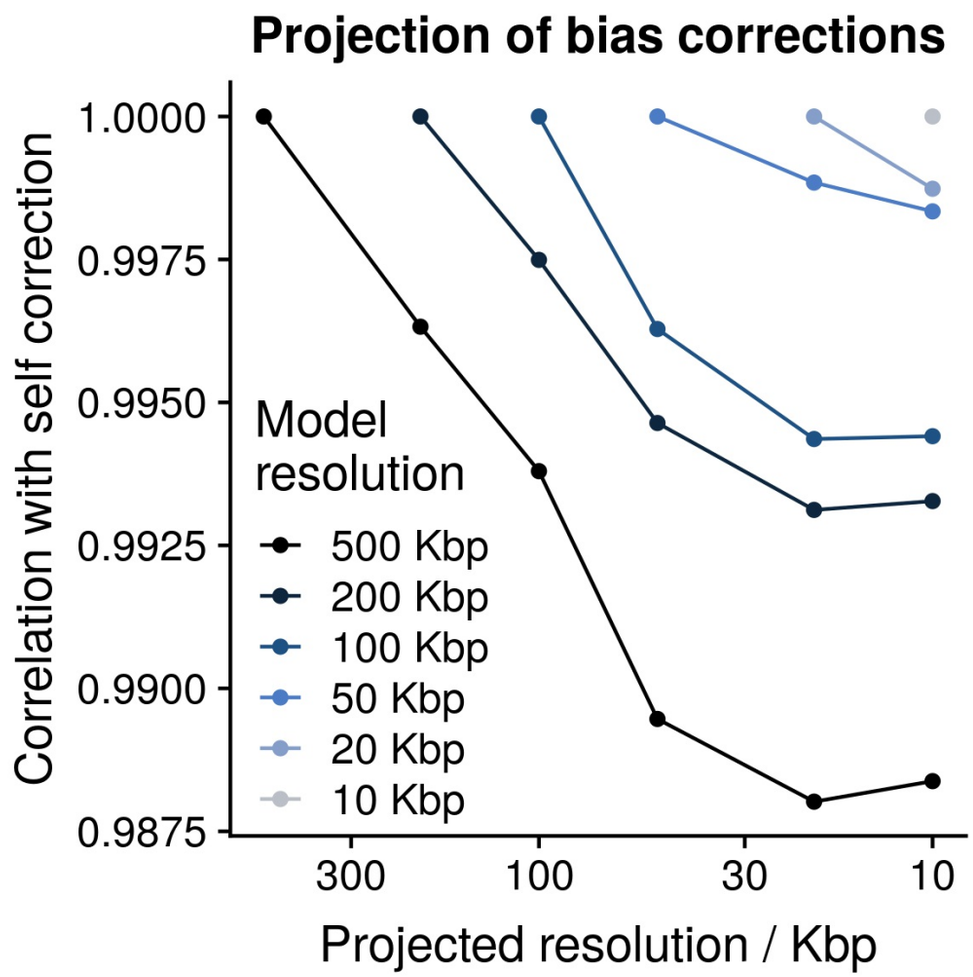
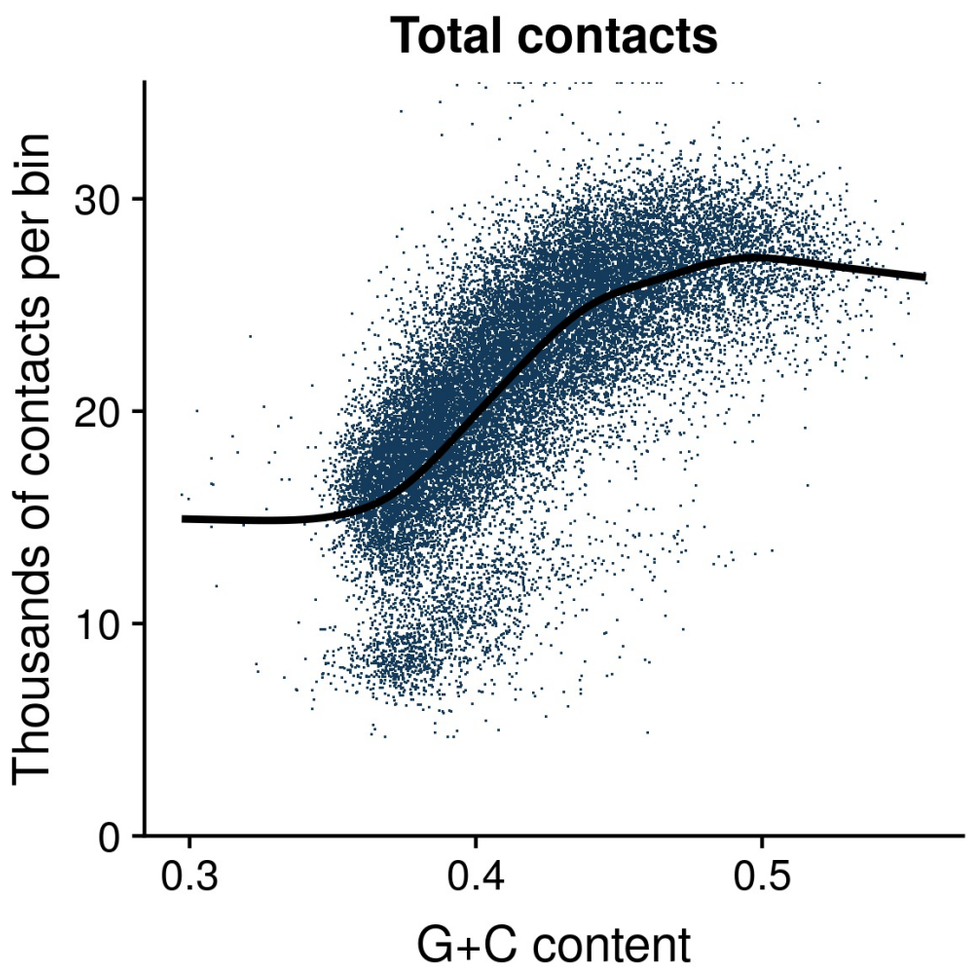
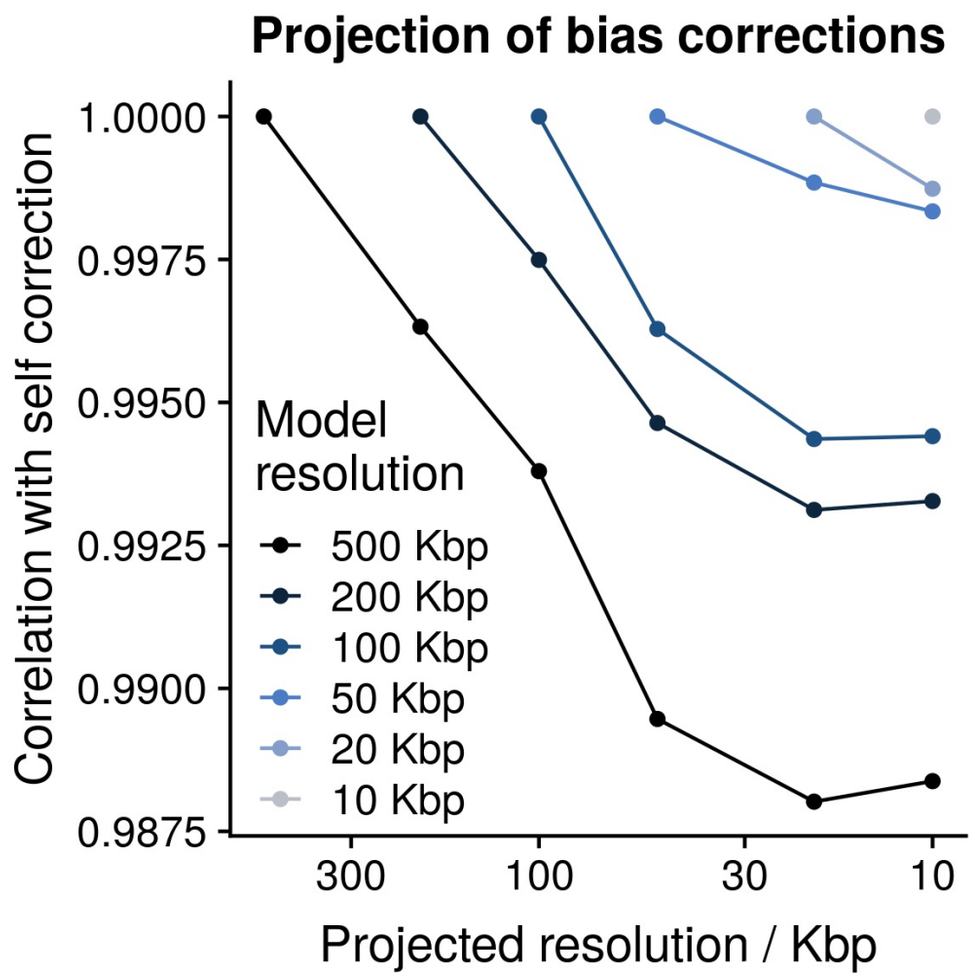




Fit once, project everywhere



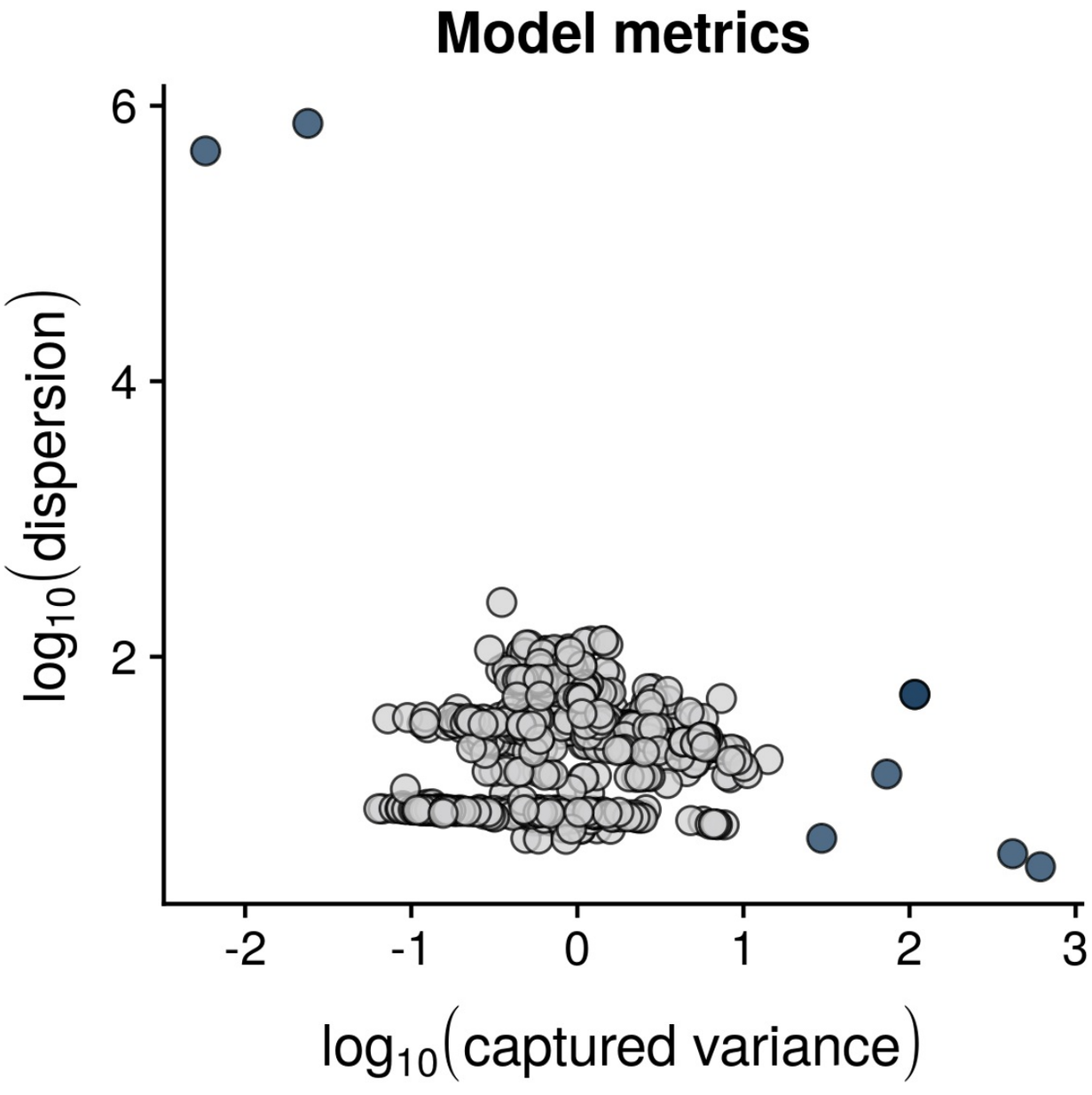


Effortless bias removal at high resolution ✓

Exploiting the model

Quality control

Model metrics as quality control



Grand summary

Grand summary

Hi-C data present biases

Grand summary

Hi-C data present biases

Use explicit modeling to reduce them

Grand summary

Hi-C data present biases

Use explicit modeling to reduce them

Exploit the model!

Grand summary

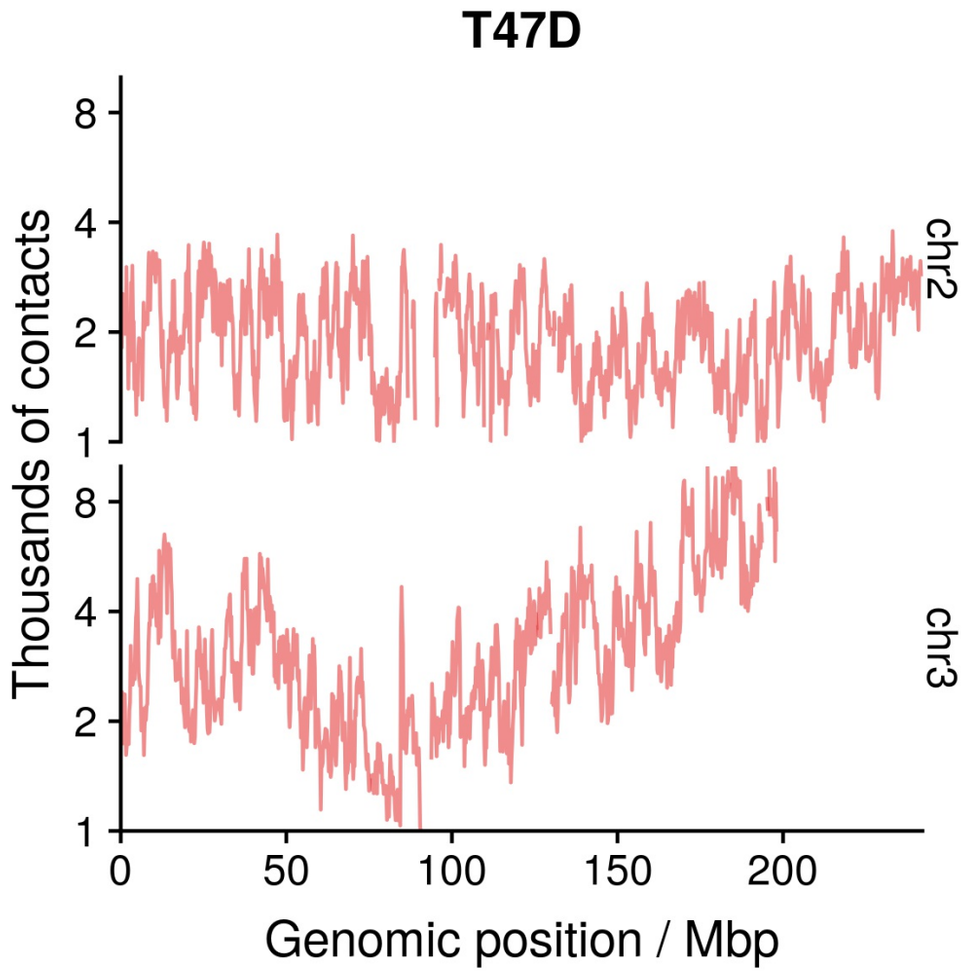
Hi-C data present biases

Use explicit modeling to reduce them

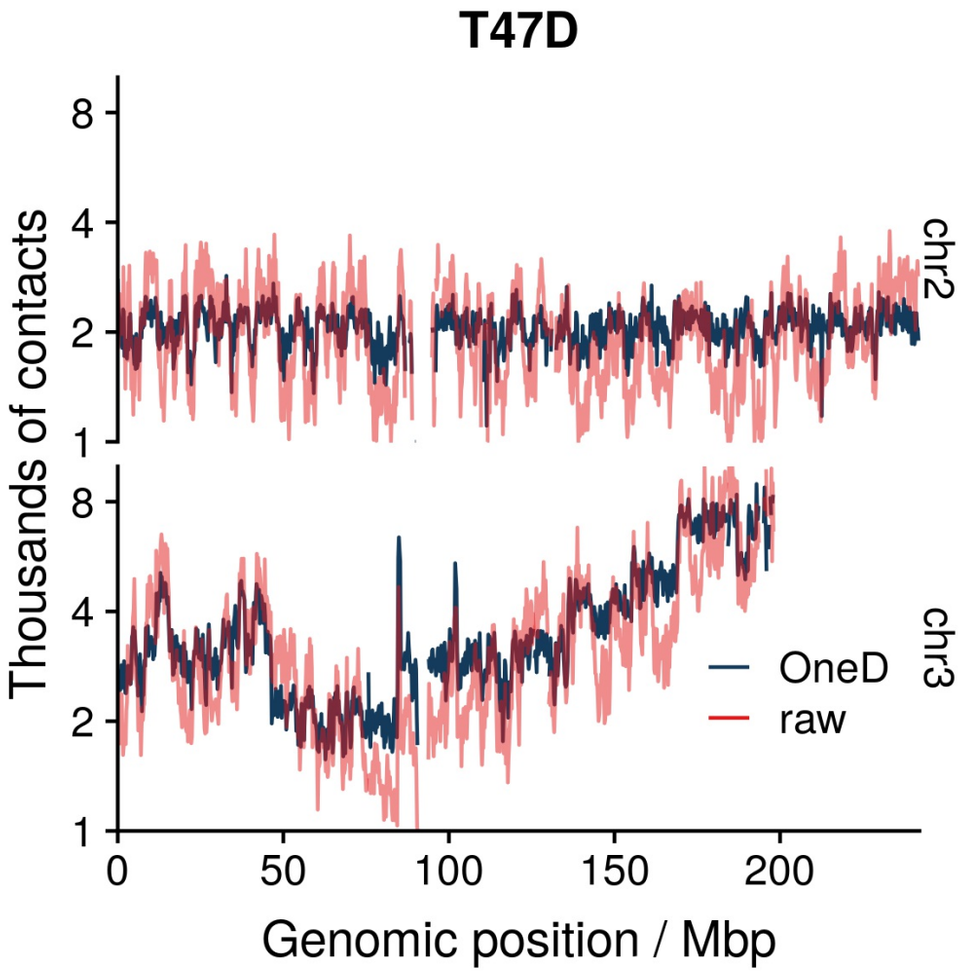
Exploit the model!

OneD: qenvio/dryhic

Total contacts → copy number



Total contacts → copy number



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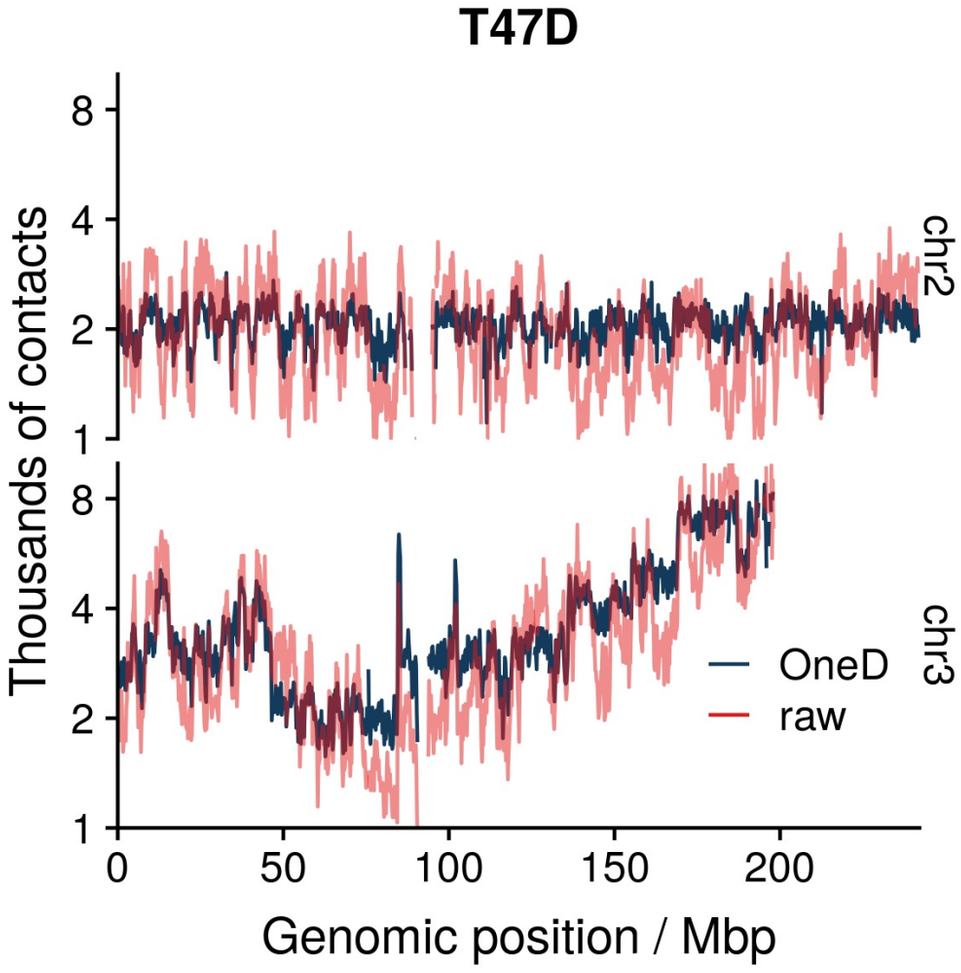
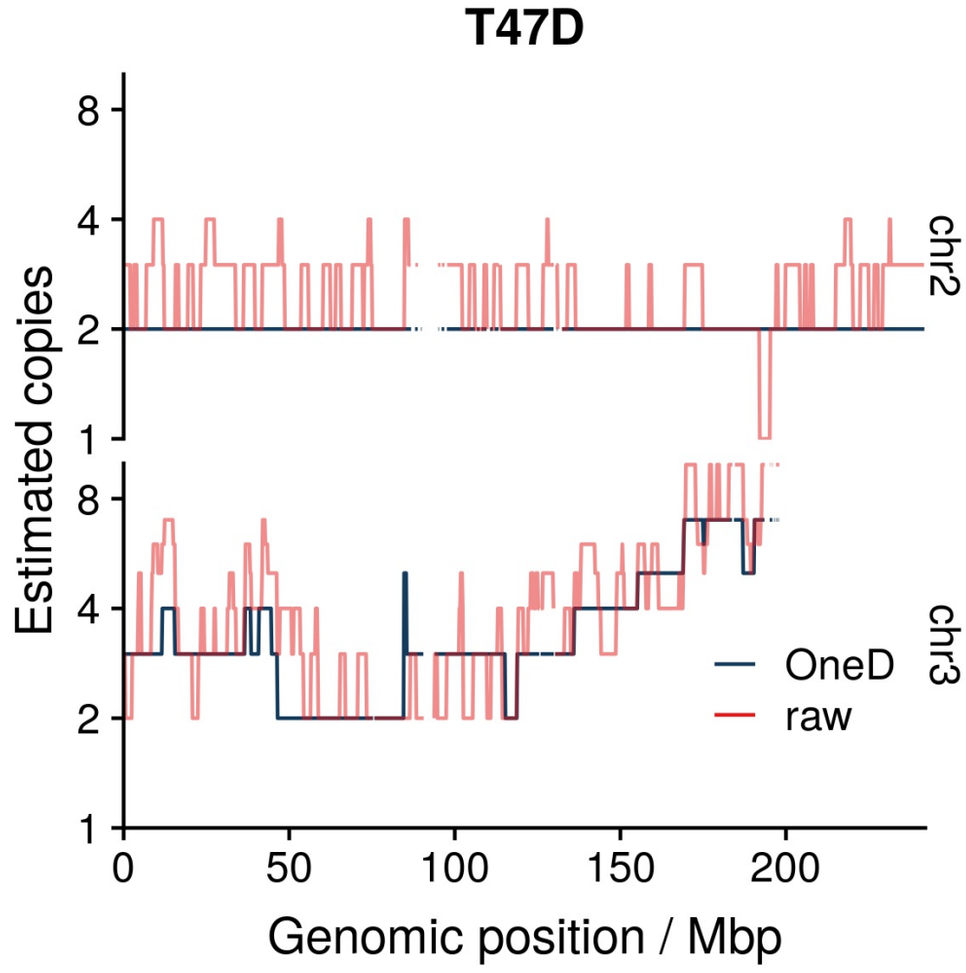
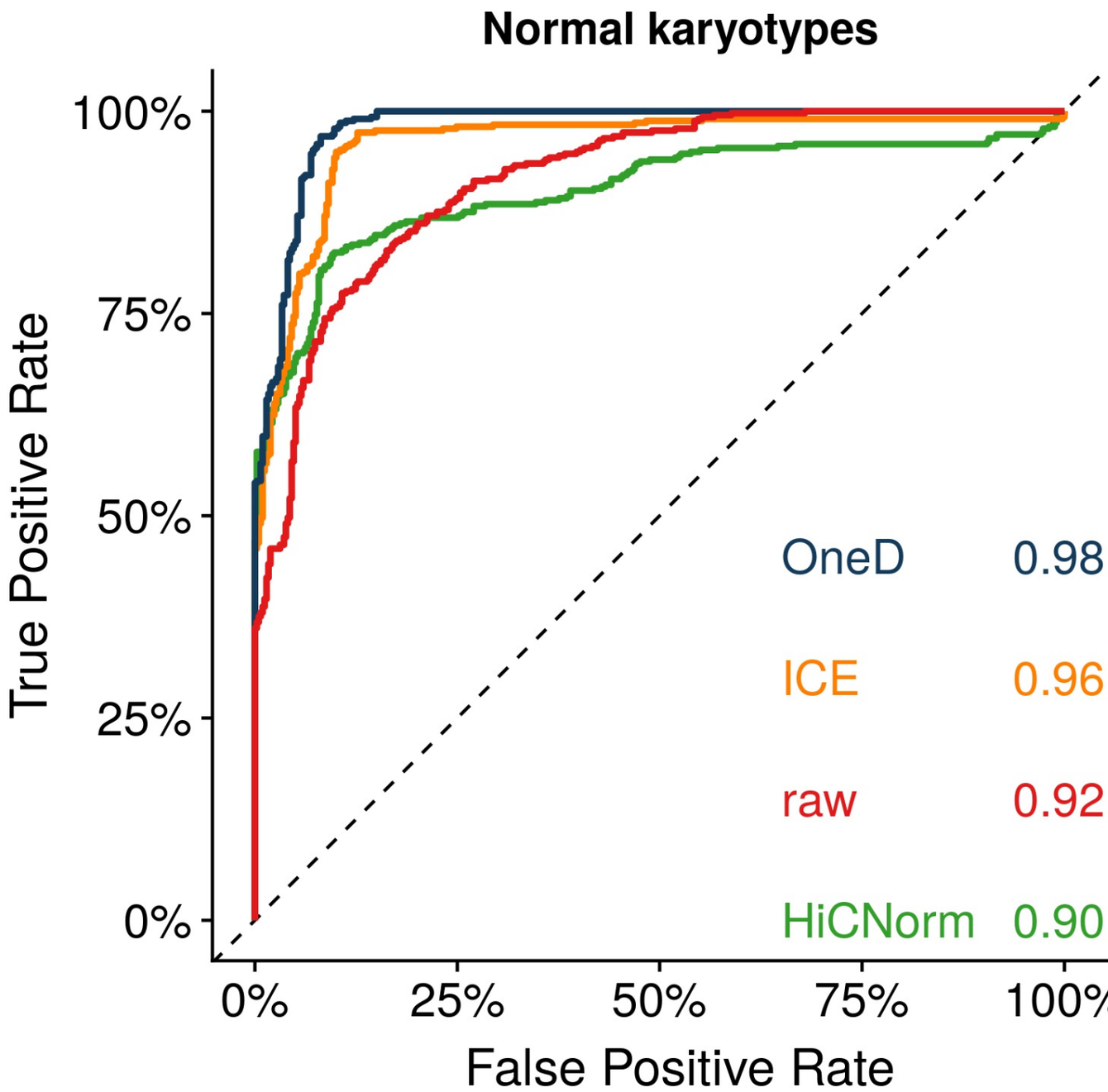
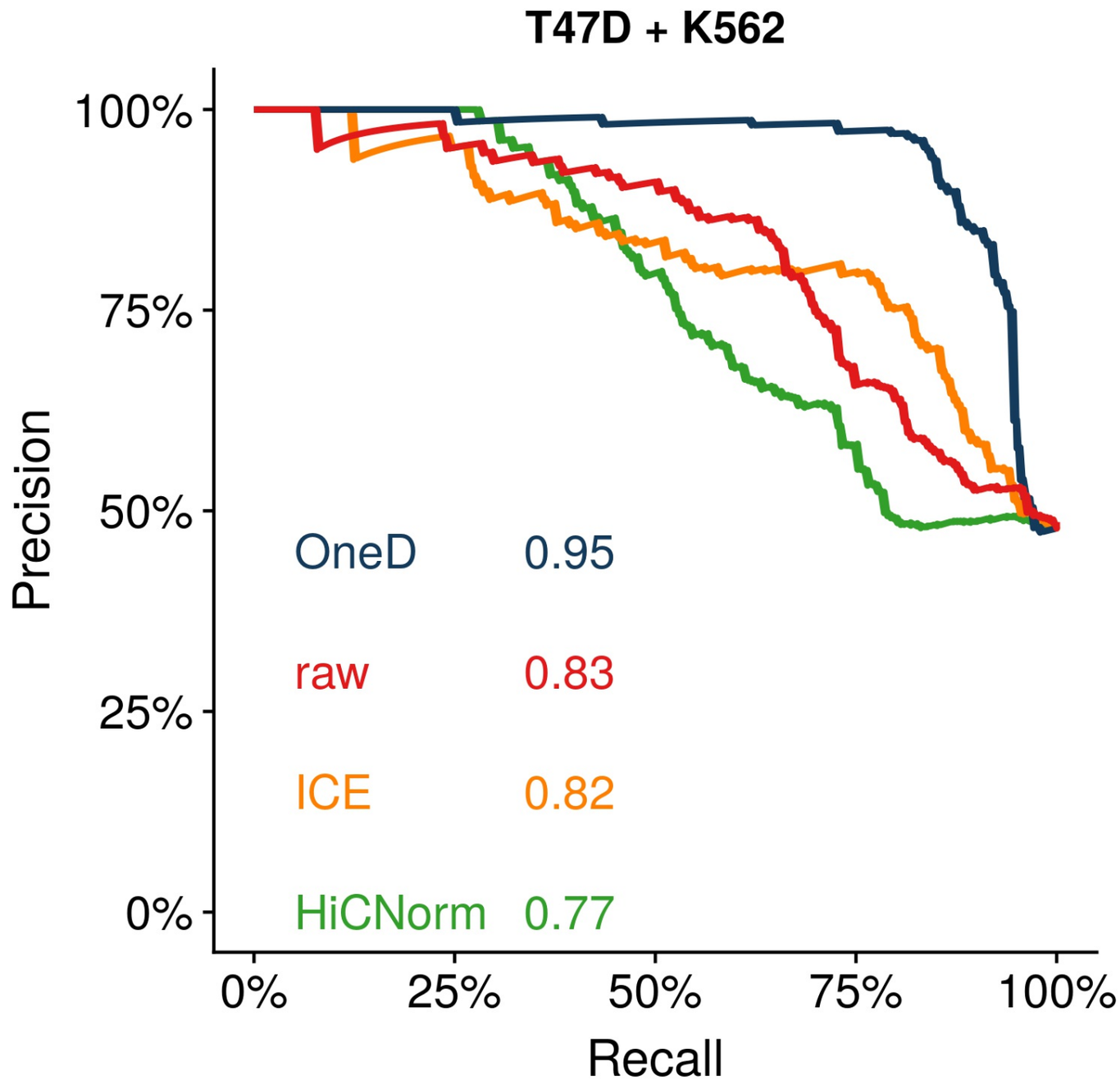




ROC and AUC normal karyotypes



PRC and AUC


T47D + K562
100%
75%
50%
25%
0%
Precision
OneD 0.95
raw 0.83
ICE 0.82
HiCNorm 0.77
0%
25%
50%
75%
100%
Recall