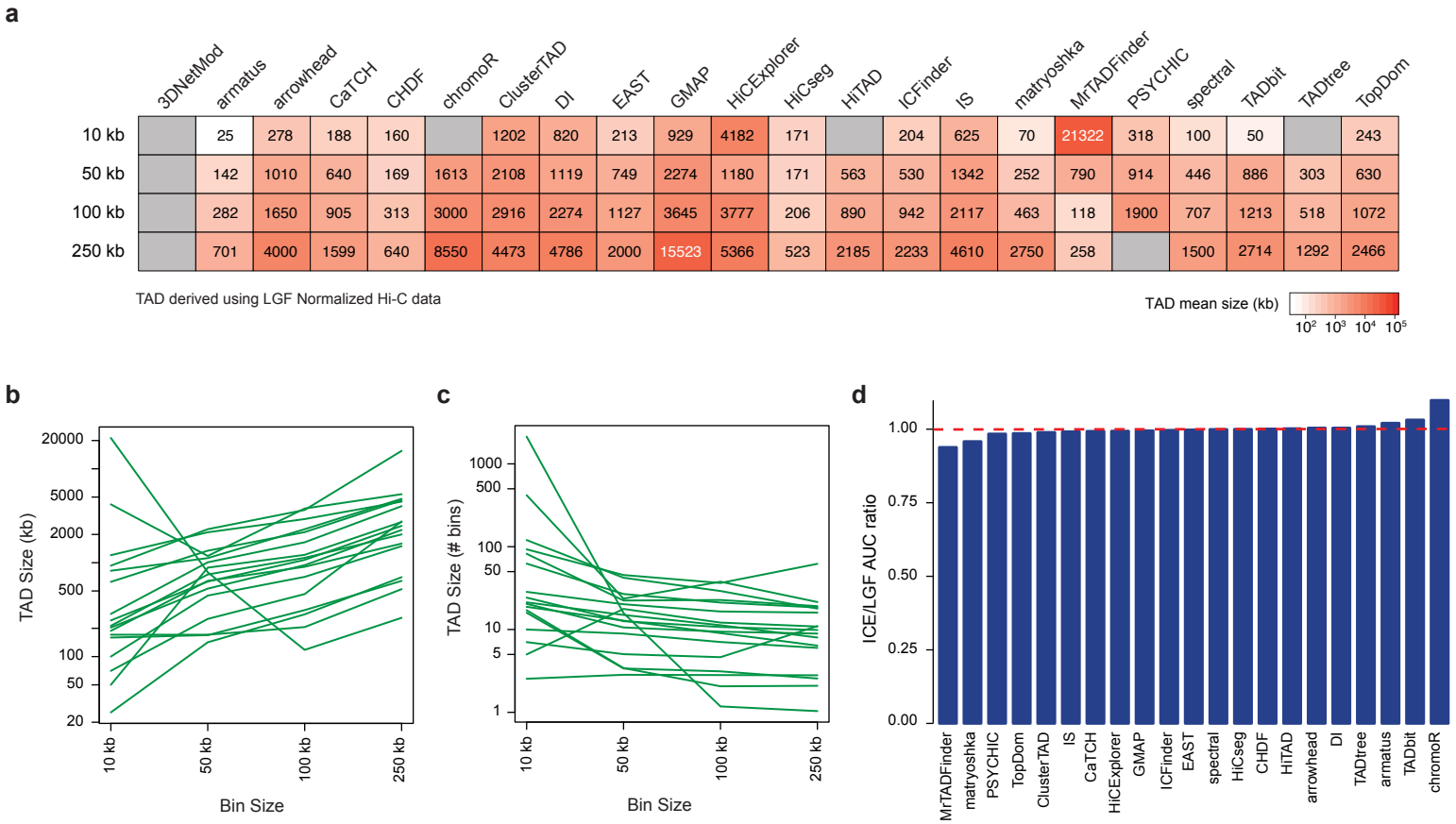
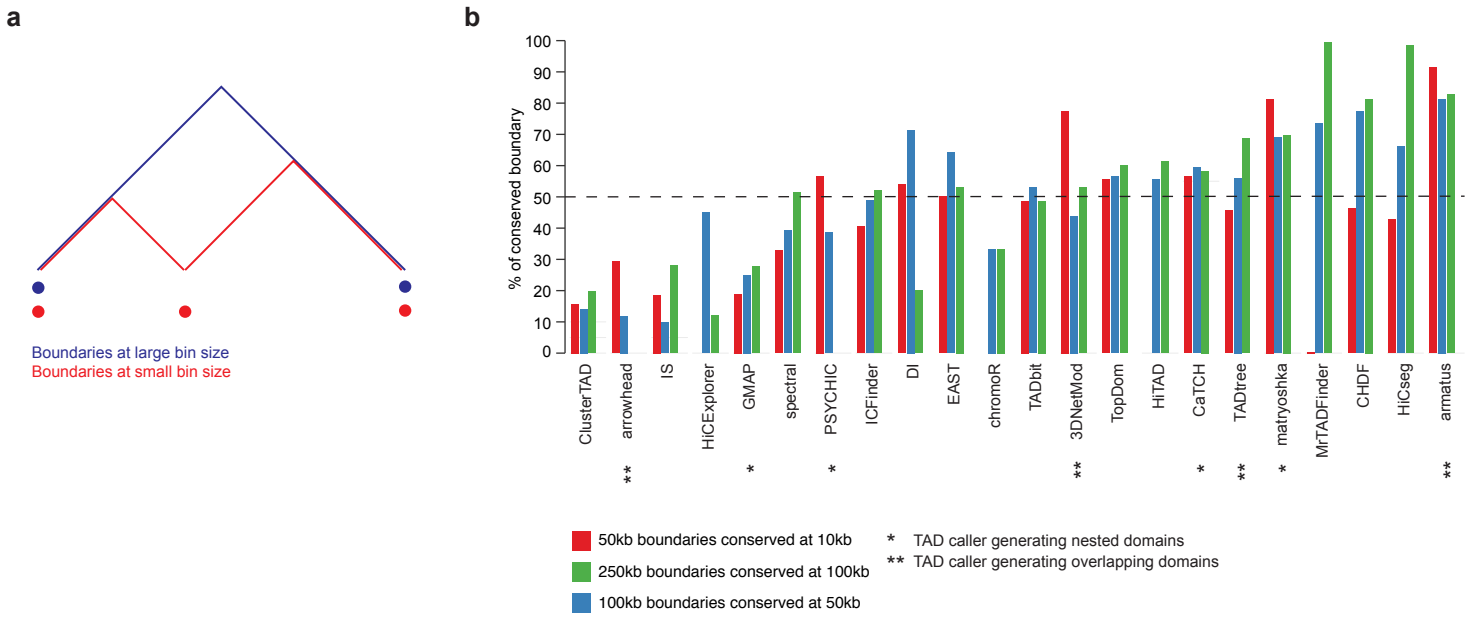


Fig S1

a) Mean size (measured in kb) of the TADs detected in the LGF-normalized Hi-C data of chromosome 4 at four different resolutions (10, 50, 100, 250kb) by each of the 22 TAD callers. Color intensity is proportional to the mean size of the TADs in log-scale, gray boxes correspond to TAD callers that did not successfully identify TADs at a given resolution.

b-c) Variation of the mean size of the TADs measured in kb **(b)** or in number of bins **(c)** across Hi-C matrix resolutions. Each line refers to a TAD caller and only TAD callers that successfully identified TADs at all 4 resolutions are shown.

d) Ratio between the Area Under the Curve (AUC) of the variation of TAD size (measured in kb – panel **b**) across matrix resolutions computed using ICE-normalized Hi-C data and the AUC computed using LGF-normalized Hi-C data.



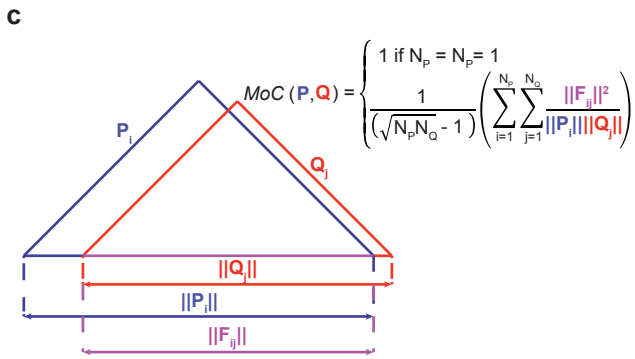


Fig S2

a) Schematic representation of nested domains: two small domains (red) are nested within a large domain (blue).

b) Percentage of boundaries identified from Hi-C matrices at 50, 100, 250kb resolution that contain a boundary identified from Hi-C matrices at, respectively, 10, 50, 100kb resolution. TAD callers are ordered from left to right by increasing mean percentage. TAD callers that return nested TADs are annotated by an asterisk at the bottom.

c) Schematic representation of the calculation of the Measure of Concordance (MoC).

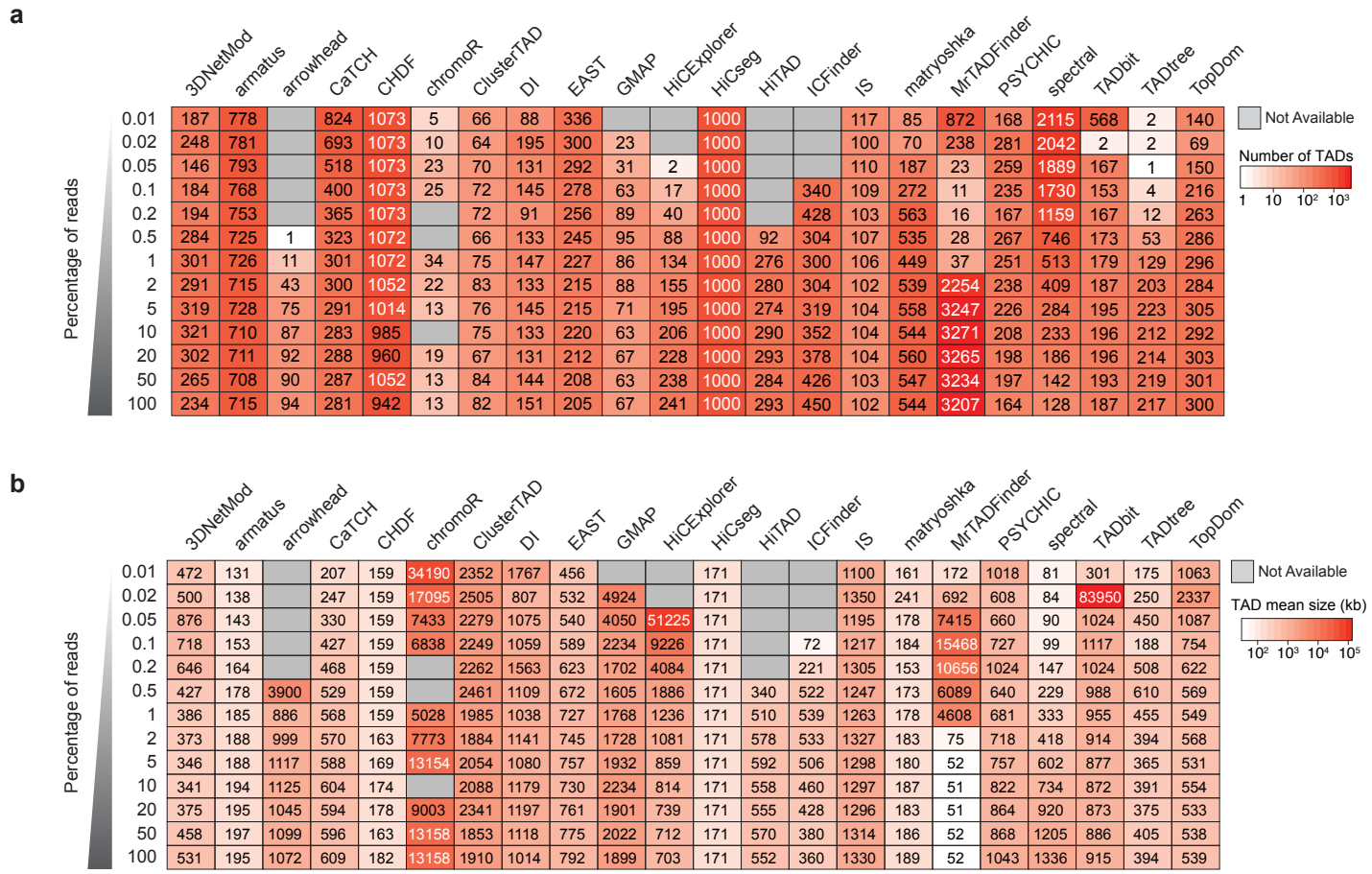


Fig S3

a-b) Total number **(a)** and mean size **(b)** of TADs detected in the ICE-normalized 50kb-bin Hi-C data of chromosome 6 for increasing sequencing depth (percentage of reads retained from the full list of contacts is indicated by the on the left).

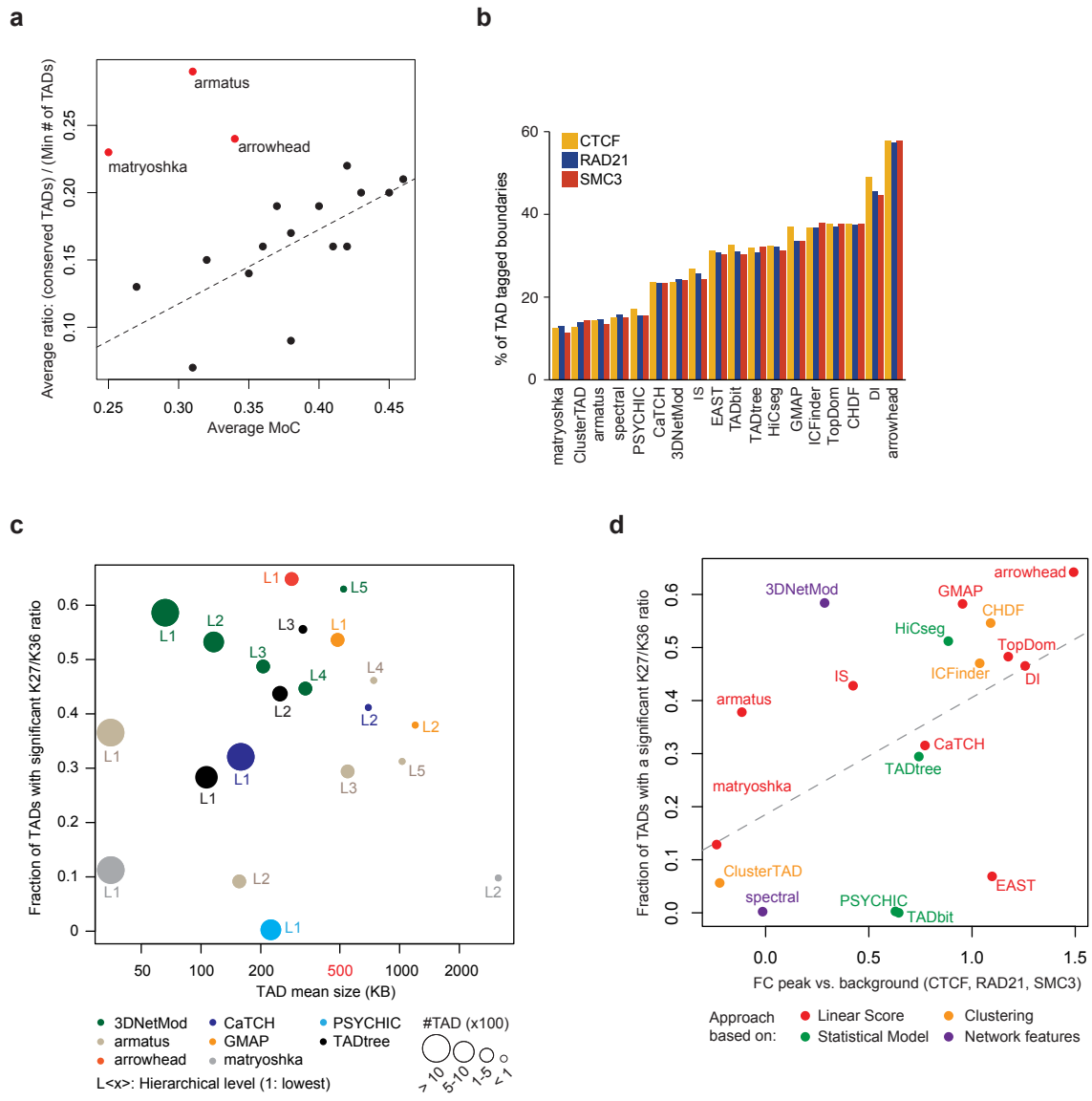


Fig S4

a) For each pair of TAD callers, ratios between number of conserved TADs and the smallest number of TADs identified by the two callers were computed. Average ratios for each TAD caller (Y-axis) are compared to the average Measure of Concordance (MoC) obtained by each TAD caller (X-axis). The dashed line is the linear fit of the values, excluding TAD callers in red (matryoshka, arrowhead, armatus).

b) Percentages of TAD boundaries tagged by CTCF (orange bar), RAD21 (blue bar) or SMC3 (red bar) proteins. TAD callers are ordered from left to right by increasing average percentage of boundaries tagged by the three proteins.

c) Fraction of TADs with significant H3K27me3 / H3K36me3 ratio vs TAD mean size for each hierarchy level of the different callers. Hierarchical levels are labeled by increasing numbers (L1, …, Ln) with L1 being the level including TADs that do not contain nested TAD. The size of the dots is proportional to the number of TADs.

d) Average fold-change (FC) of peak signals of structural proteins (CTCF, RAD21 and SMC3) (X-axis) versus fraction of TADs with significant H3K27me3/H3K36me3 log10-ratio (Y-axis). TAD callers are color coded according to the general approach they adopted. The dashed line indicates the linear fit.

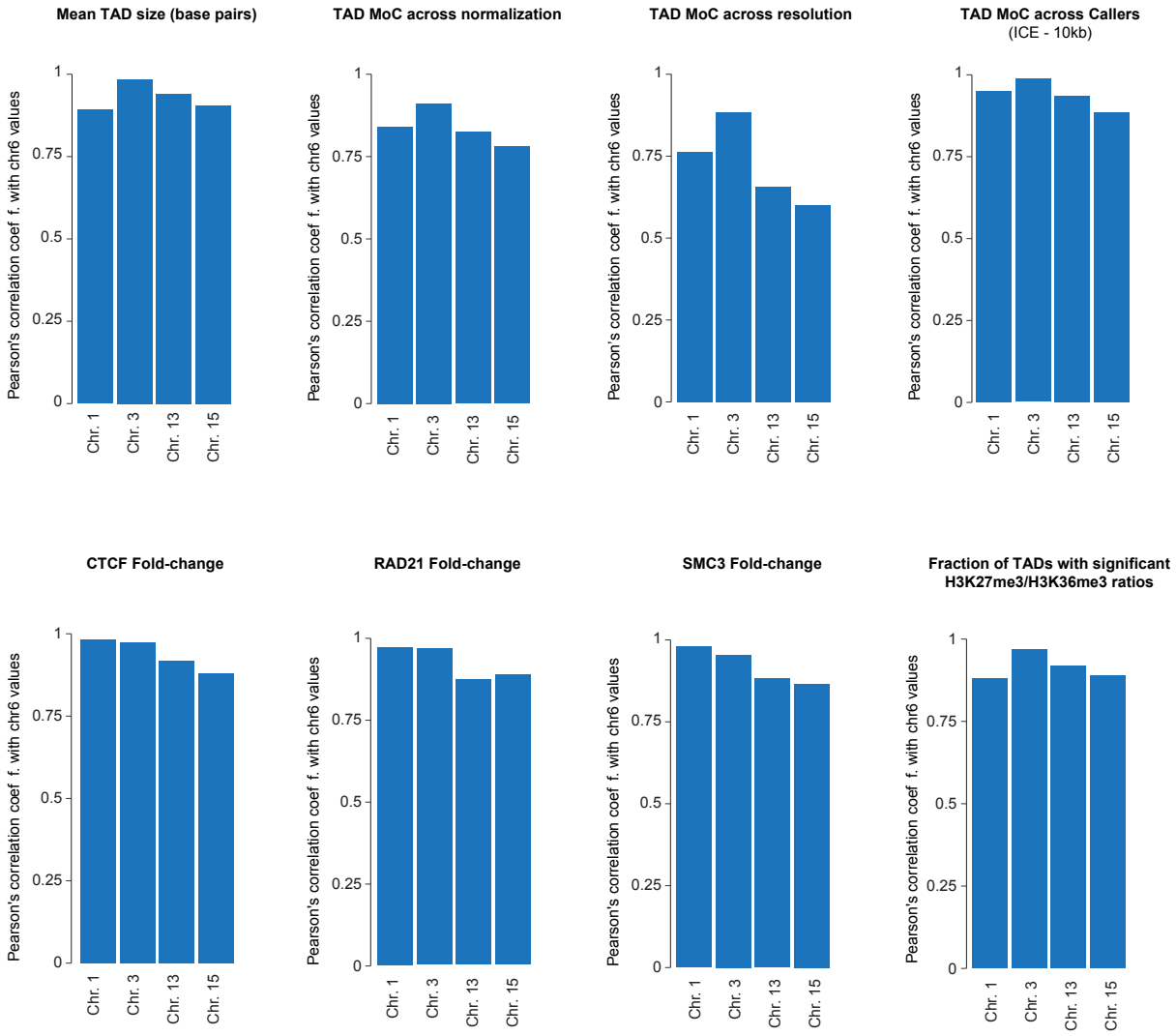


Fig S5

Pearson's correlation coefficients between the results obtained for chromosome 6 and those obtained for chromosomes 1, 3, 13, and 15 for the following analyses (from top left to bottom right): mean TAD size (measured in base pairs), Measure of Concordance (MoC) across normalizations, MoC across resolutions, MoC between TAD callers at 10kb ICE, CTCF fold-change of peak signal, RAD21 fold-change of peak signal, SMC3 fold-change of peak signal, fraction of TADs with significant H3K27me3/H3K36me3 ratios.

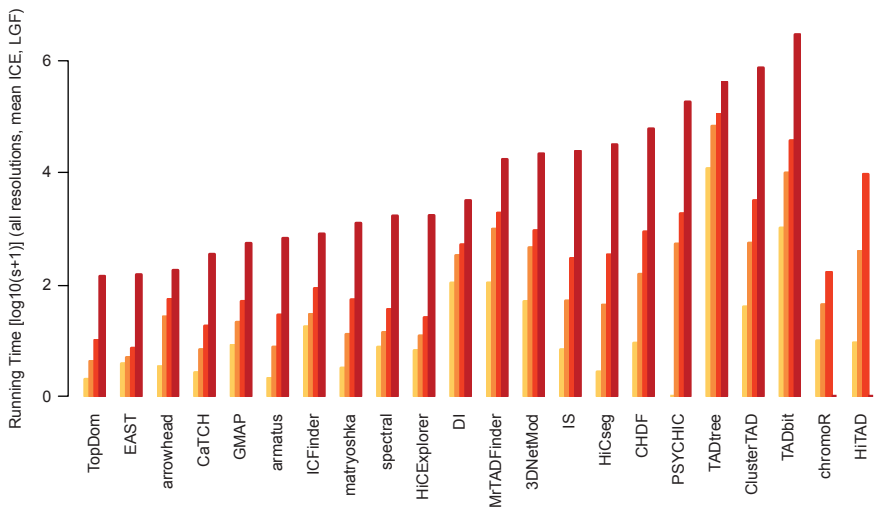


Fig S6

Running time (in log-scale) of the 22 TAD callers (ordered by increasing average value). For each TAD caller, the bars are ordered from left to right by increasing Hi-C data resolution (1000, 250, 100, 50, 10kb) and correspond to the average of the running times obtained for ICE- and LGF-normalized data.