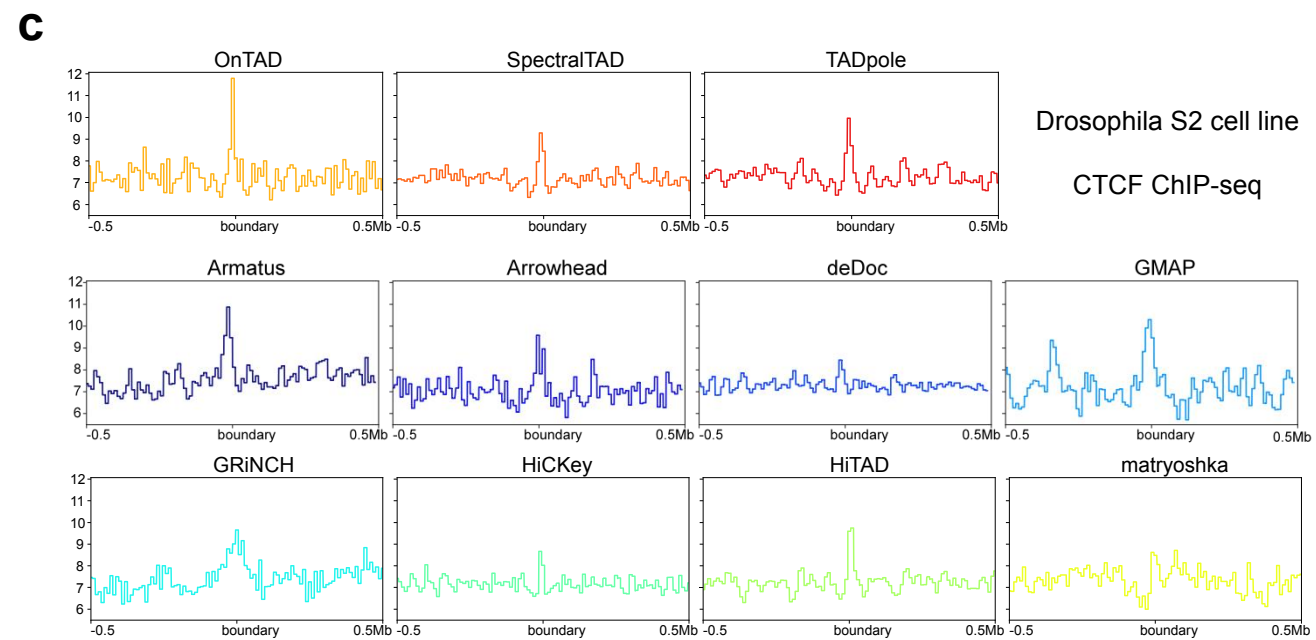
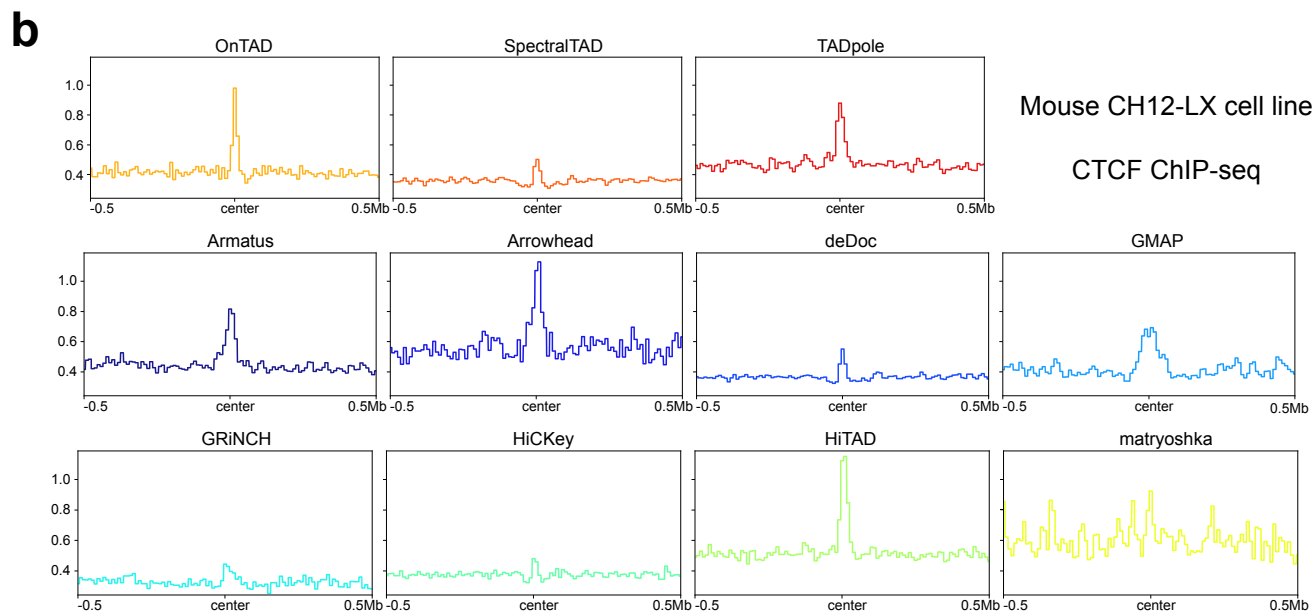
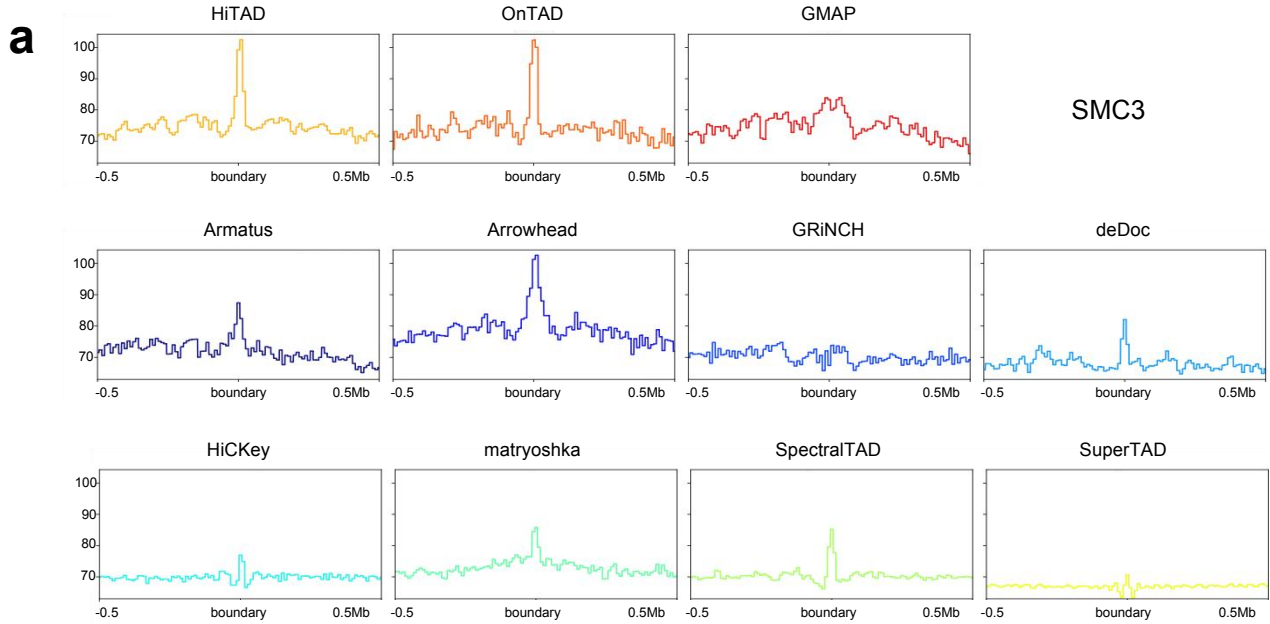
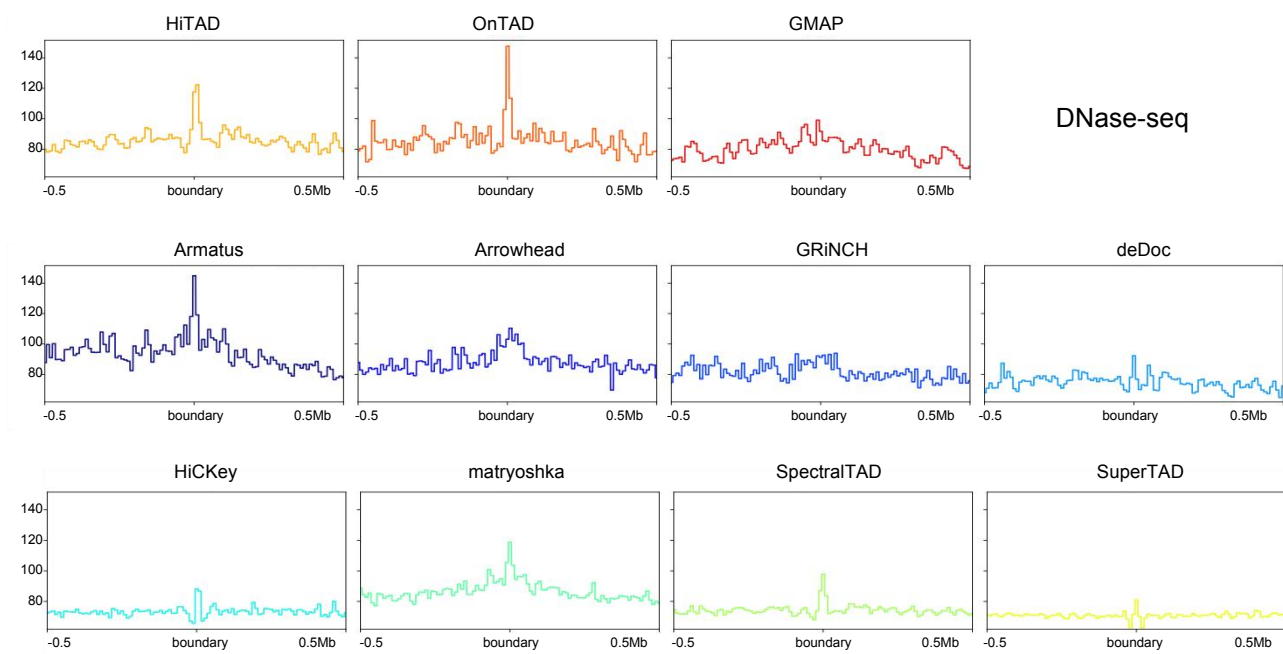
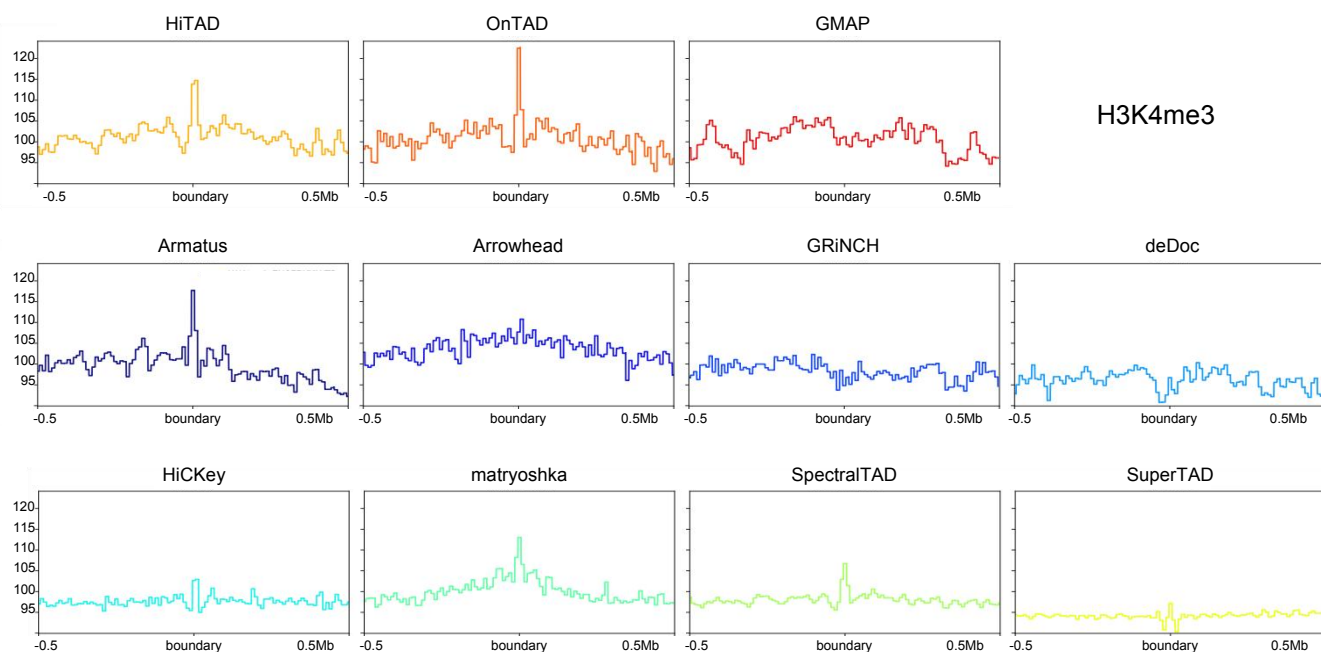
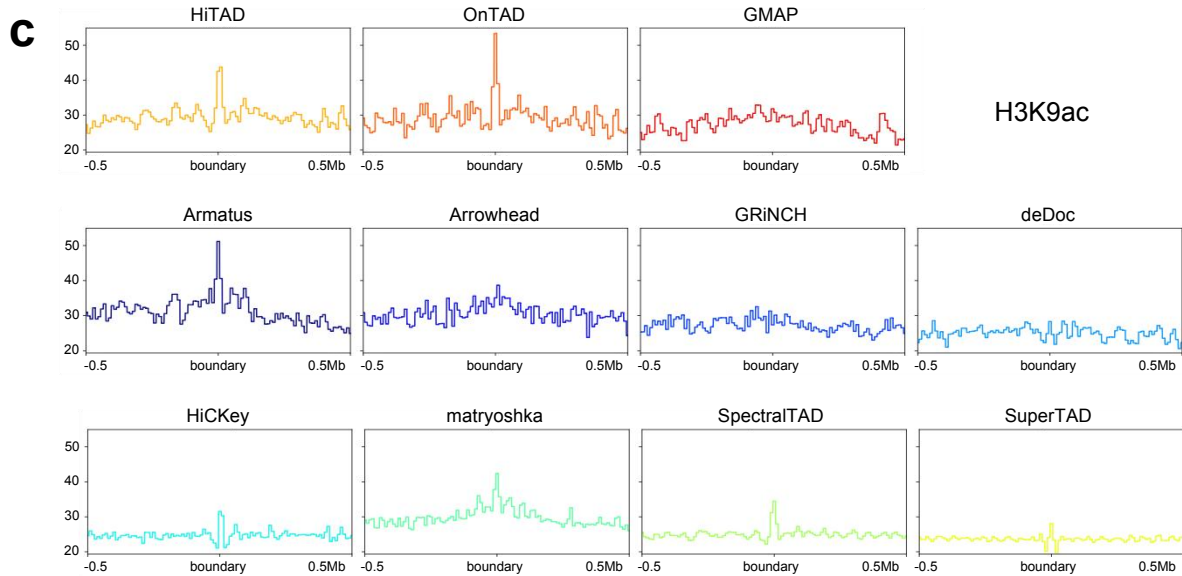
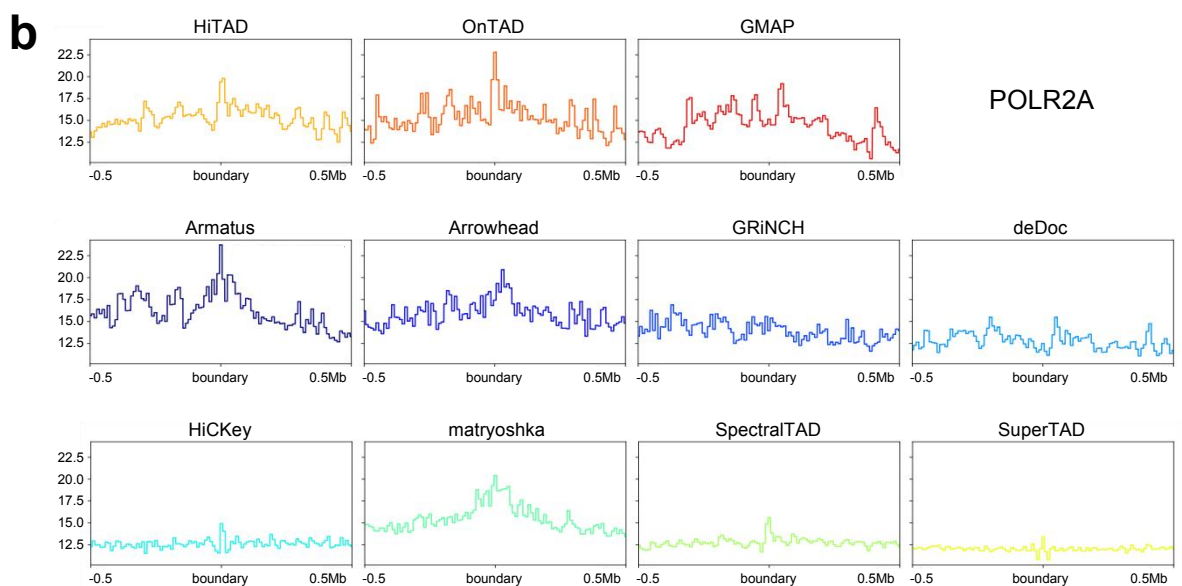
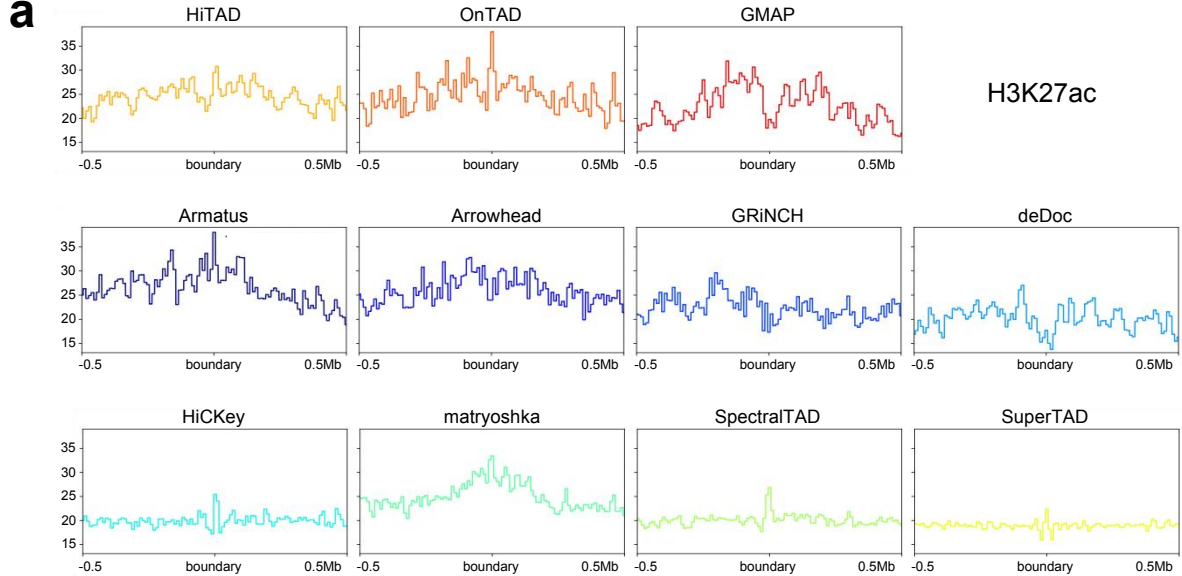


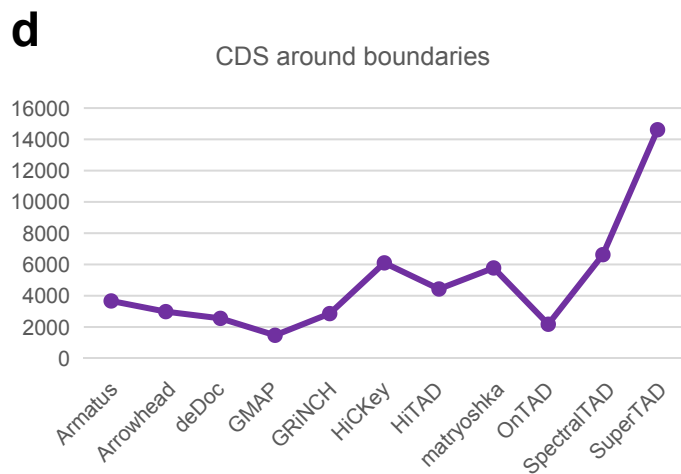
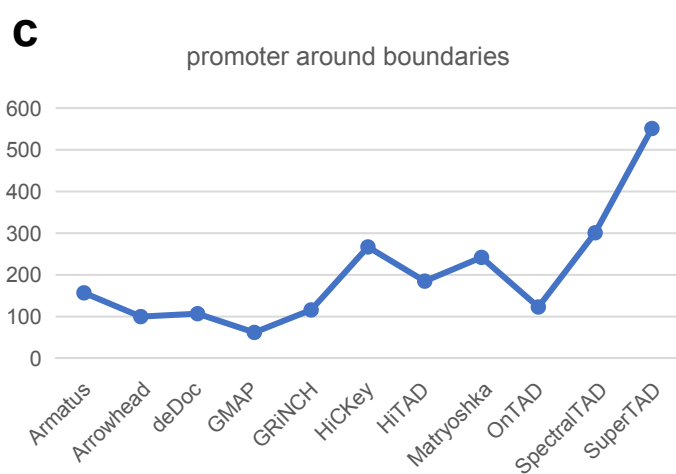
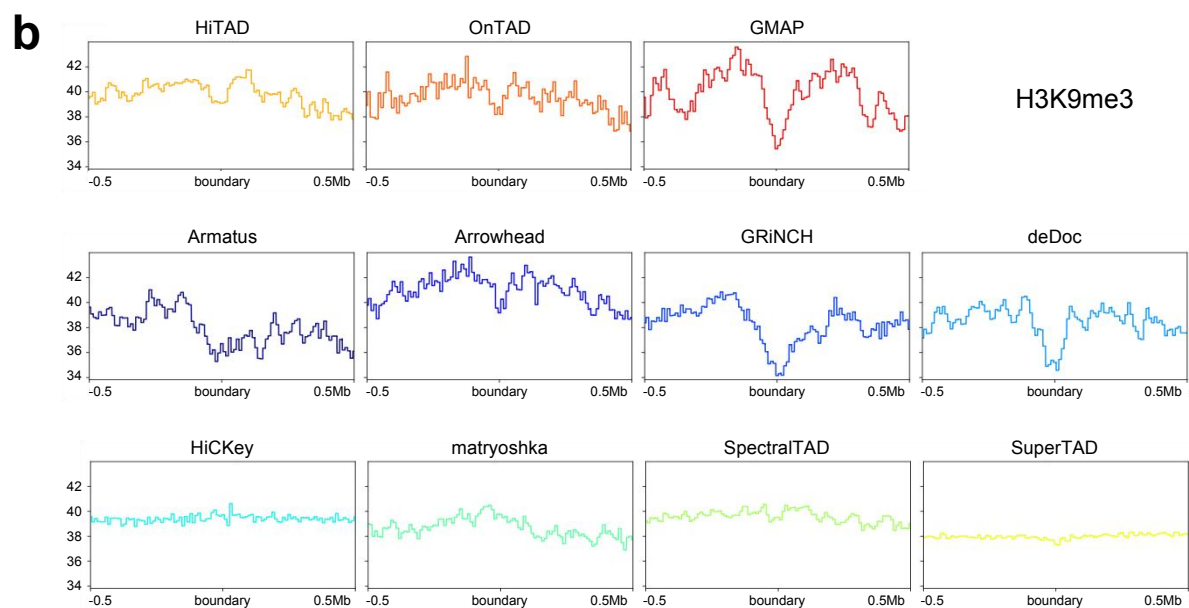
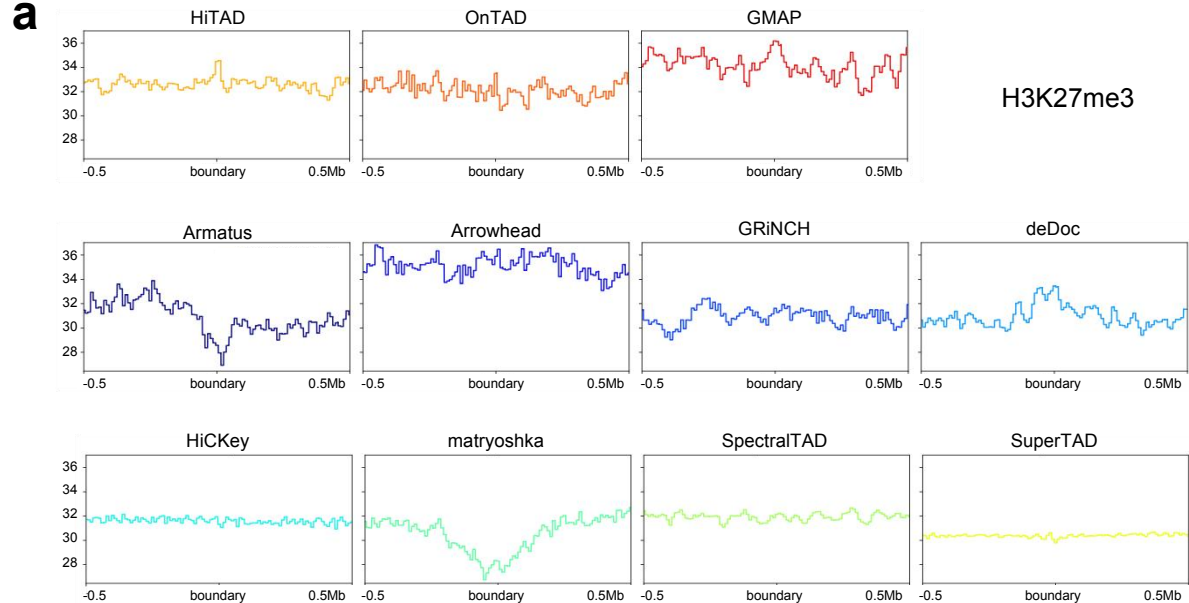


**d****e**

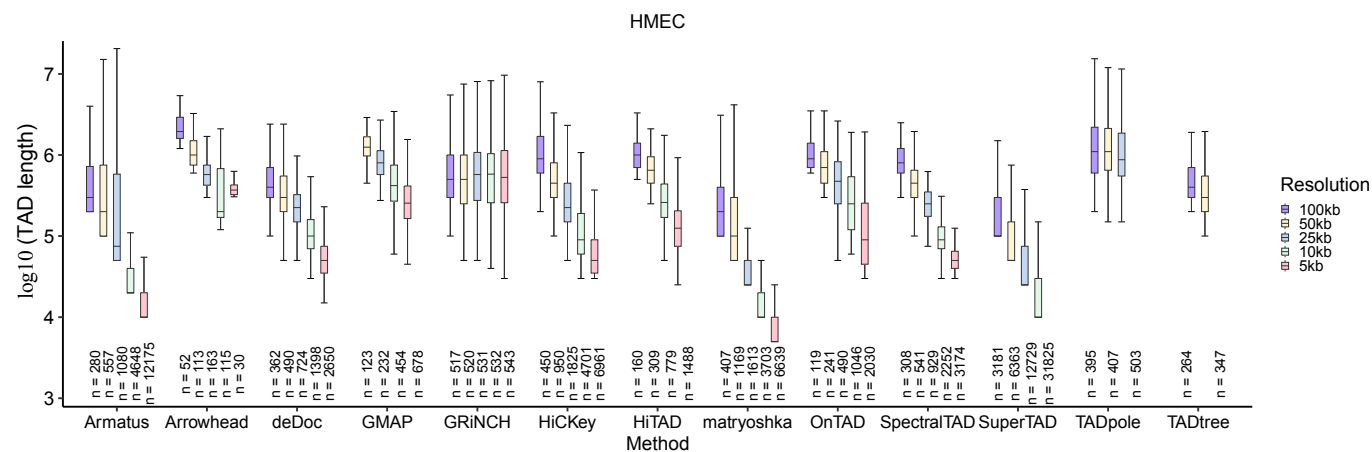
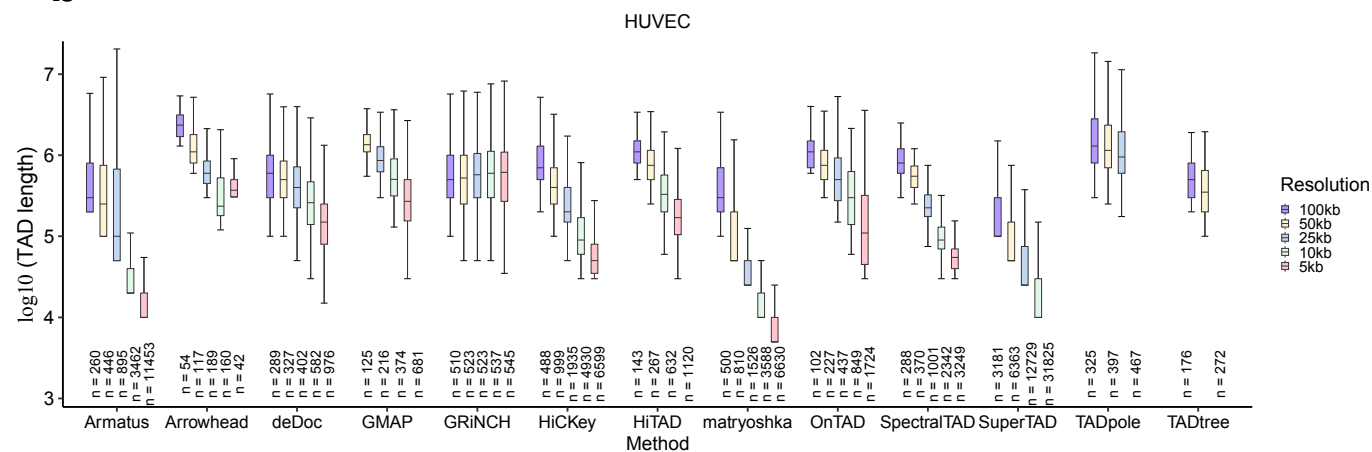
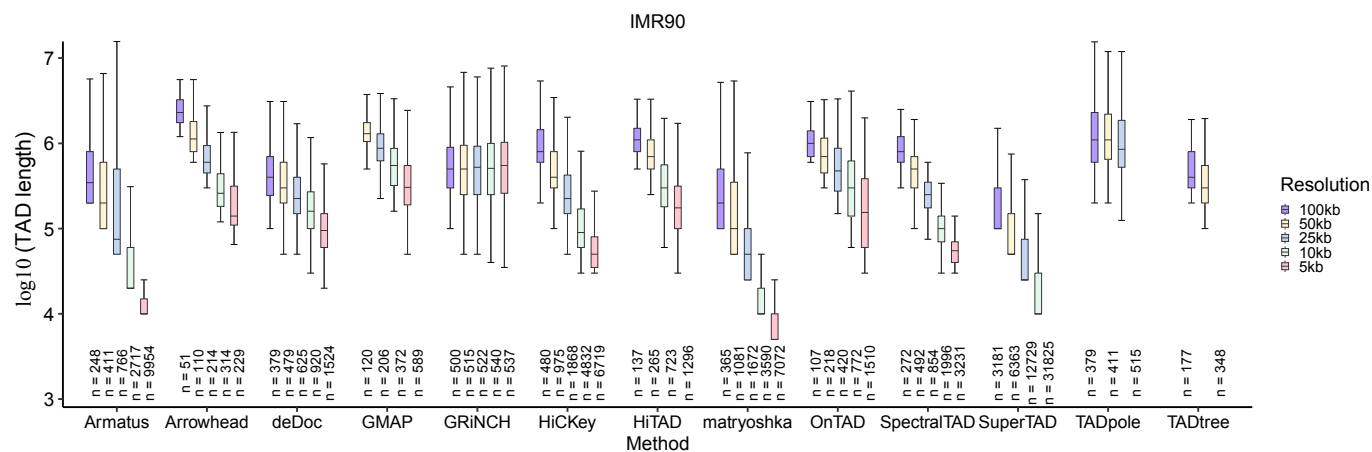
**Supplementary Figure 1. Representative examples of peak signals for (a) SMC3 (b) CTCF in mouse CH12-LX cell line (c) CTCF in drosophila S2 cell line (d) DNase-seq and (e) H3K4me3.**

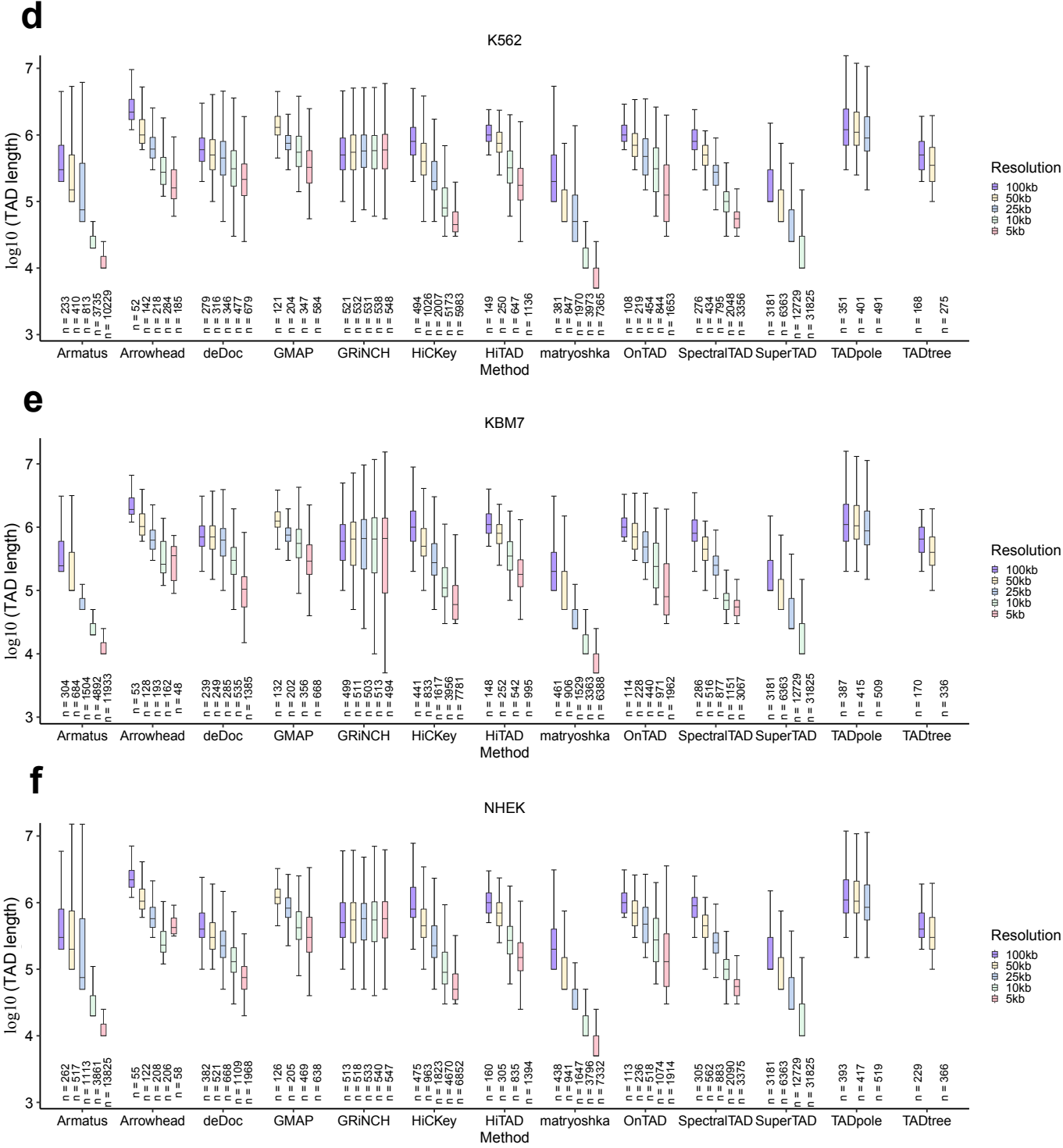


**Supplementary Figure 2. Representative examples of ChIP-seq peak signals for (a) H3K27ac (b) POLR2A and (c) H3K9ac.**



**Supplementary Figure 3. Representative examples of ChIP-seq peak signals for (a) H3K27me3 (b) H3K9me3. (c) Numbers of overlap between TAD boundaries and (c) promoter or (d) CDS**

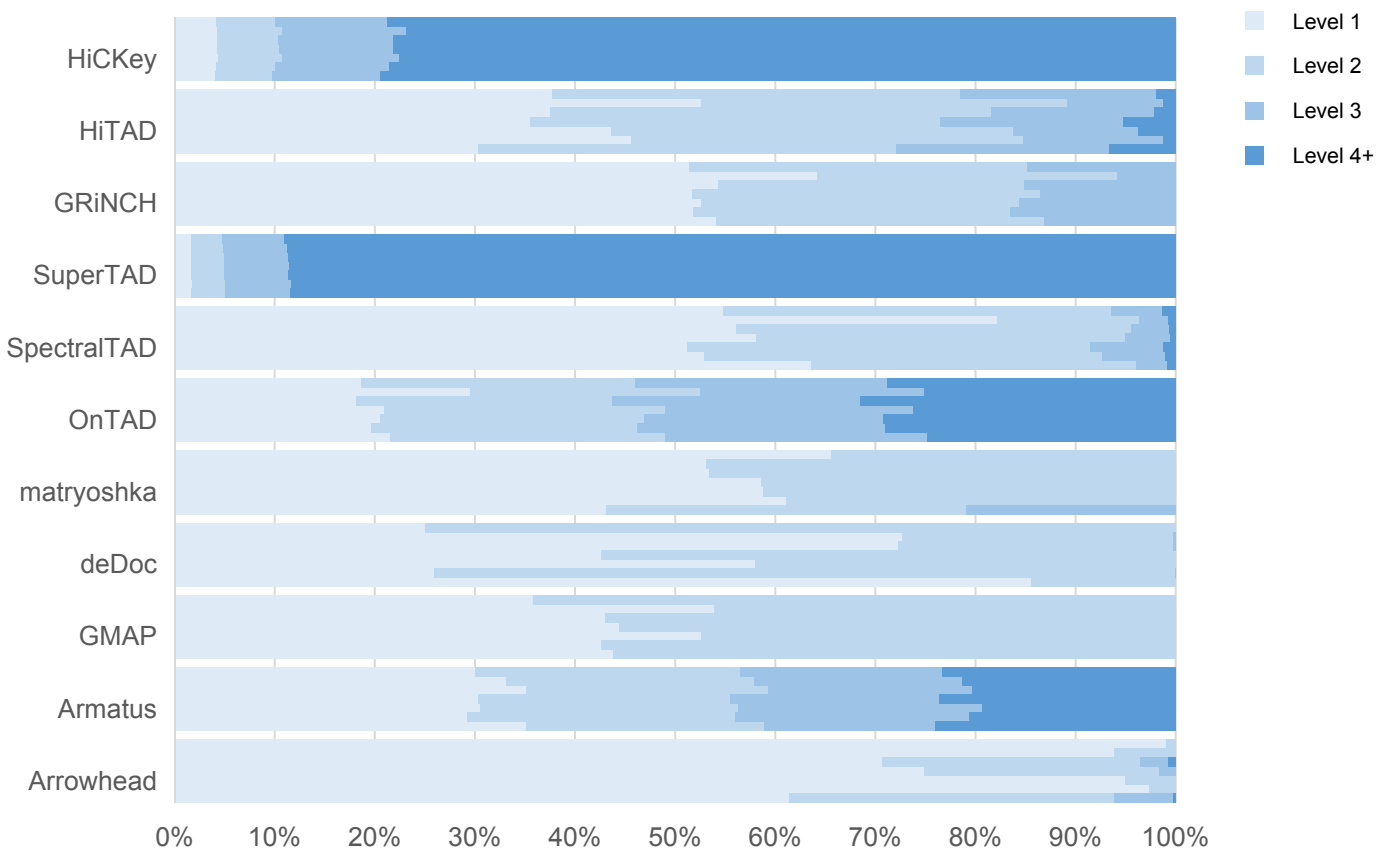
**a****b****c**



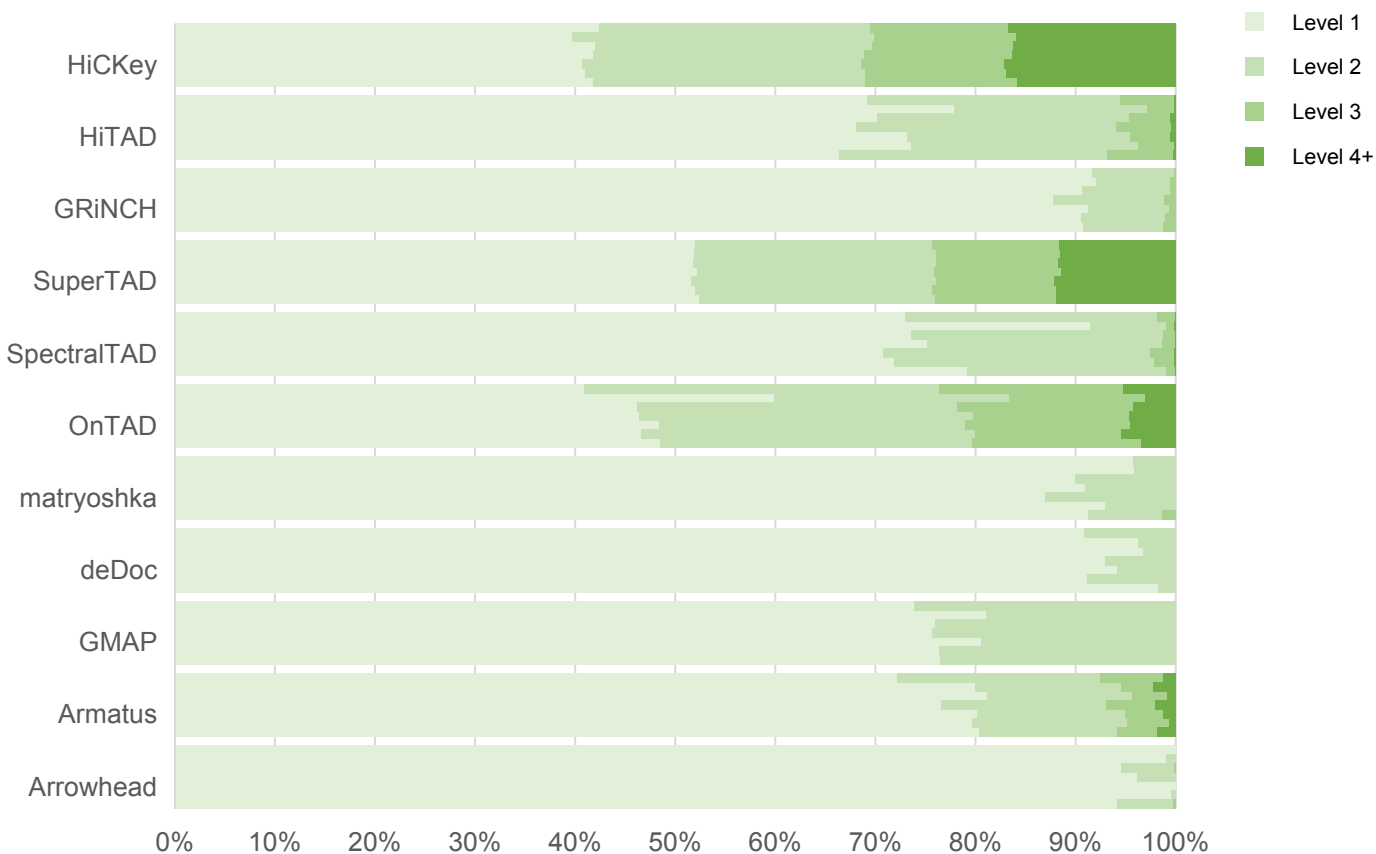
**Supplementary Figure 4. TAD size range at various resolutions in chromosome 7 of ICE-normalized Hi-C data.** The line that divides the box into 2 parts represents the median of the data. The ends of the box shows the upper (Q3) and lower (Q1) quartiles. The difference between Quartiles 1 and 3 is called the interquartile range (IQR). The extreme line shows Q3+1.5xIQR to Q1-1.5xIQR (the highest and lowest value excluding outliers). These graphs are from the following cell lines: (a) HMEC, (b) HUVEC, (c) IMR90, (d) K562, (e) KBM7, and (f) NHEK. Source data are provided as a Source Data file.

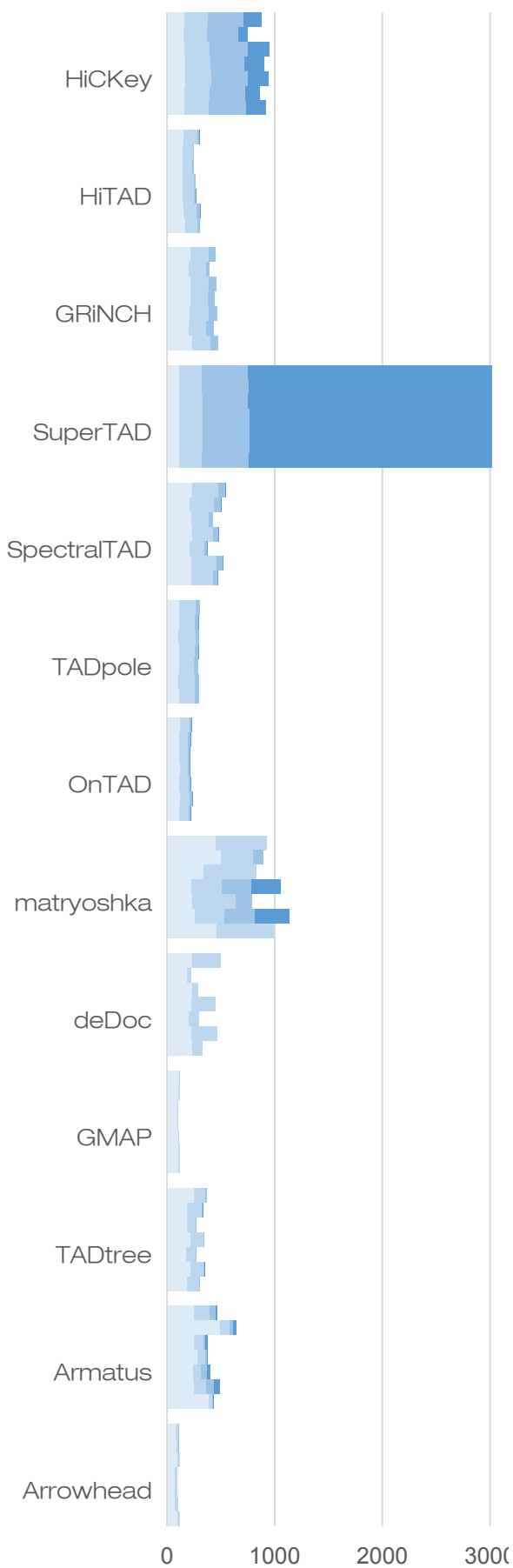
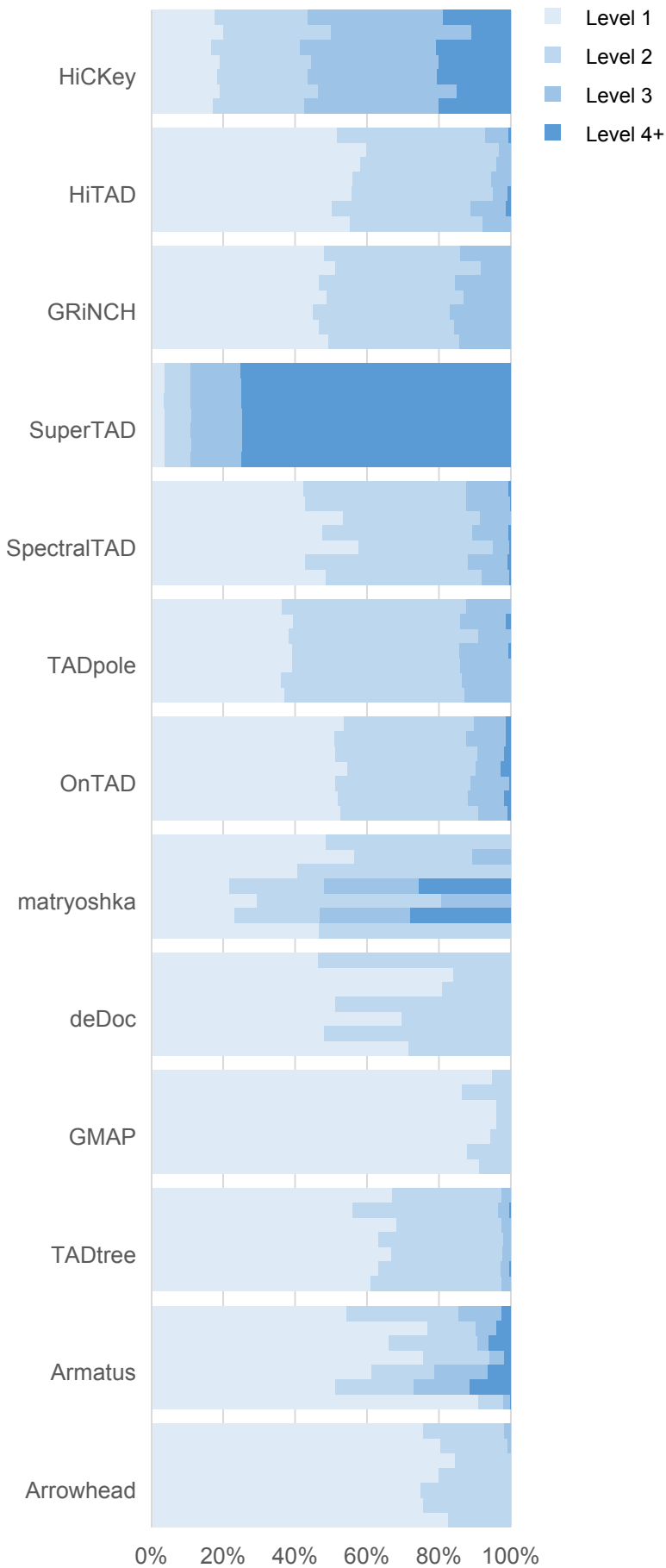
**a**

Percent of TAD region at each level

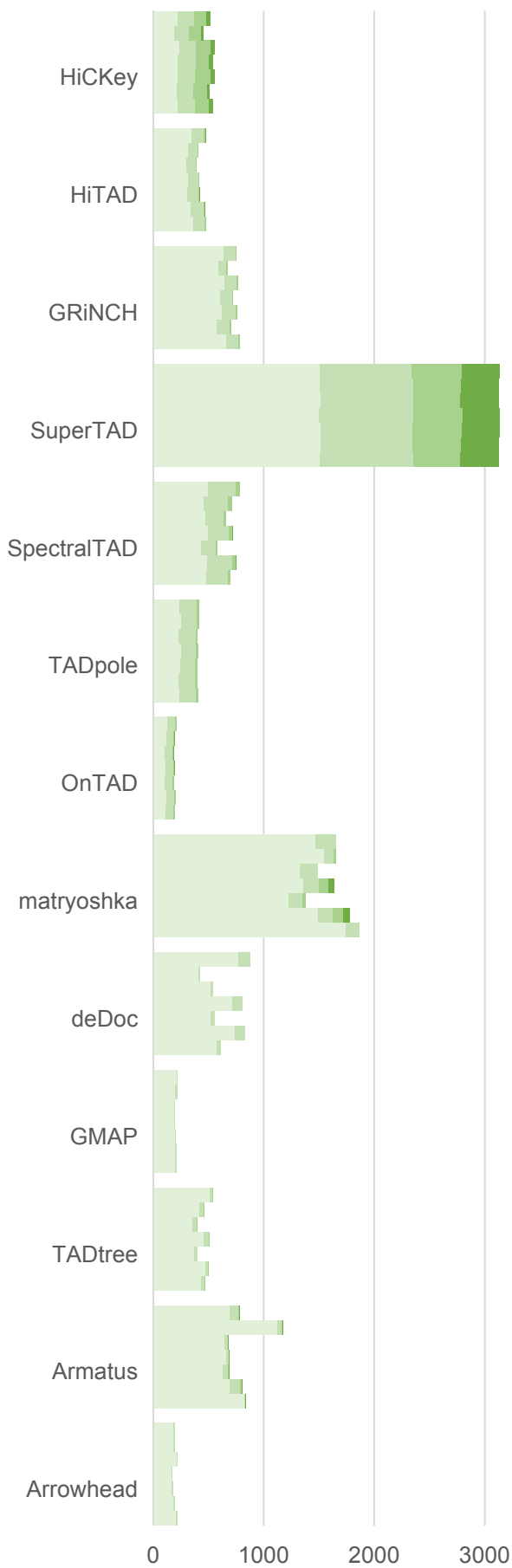
**b**

Percent of TAD boundary at each level

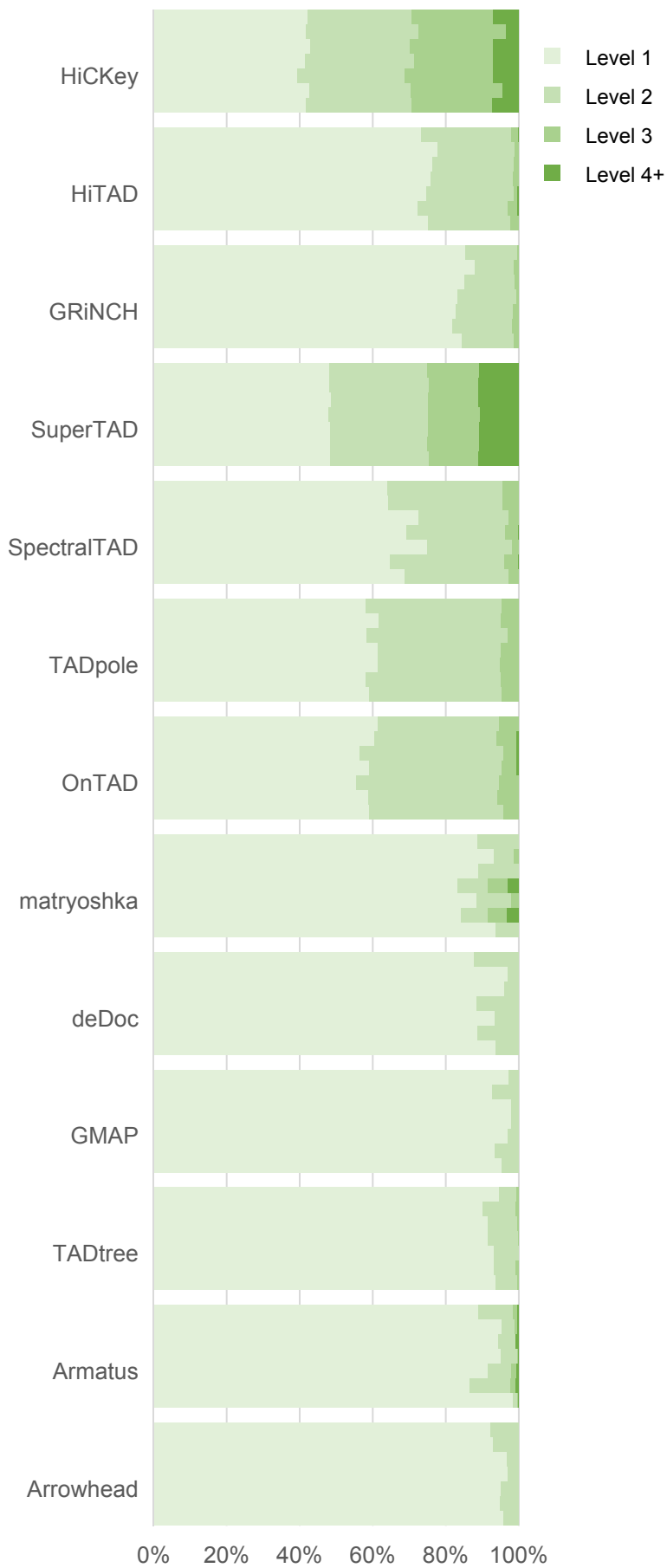


**c** Number of TAD region at each level**d** Percent of TAD region at each level

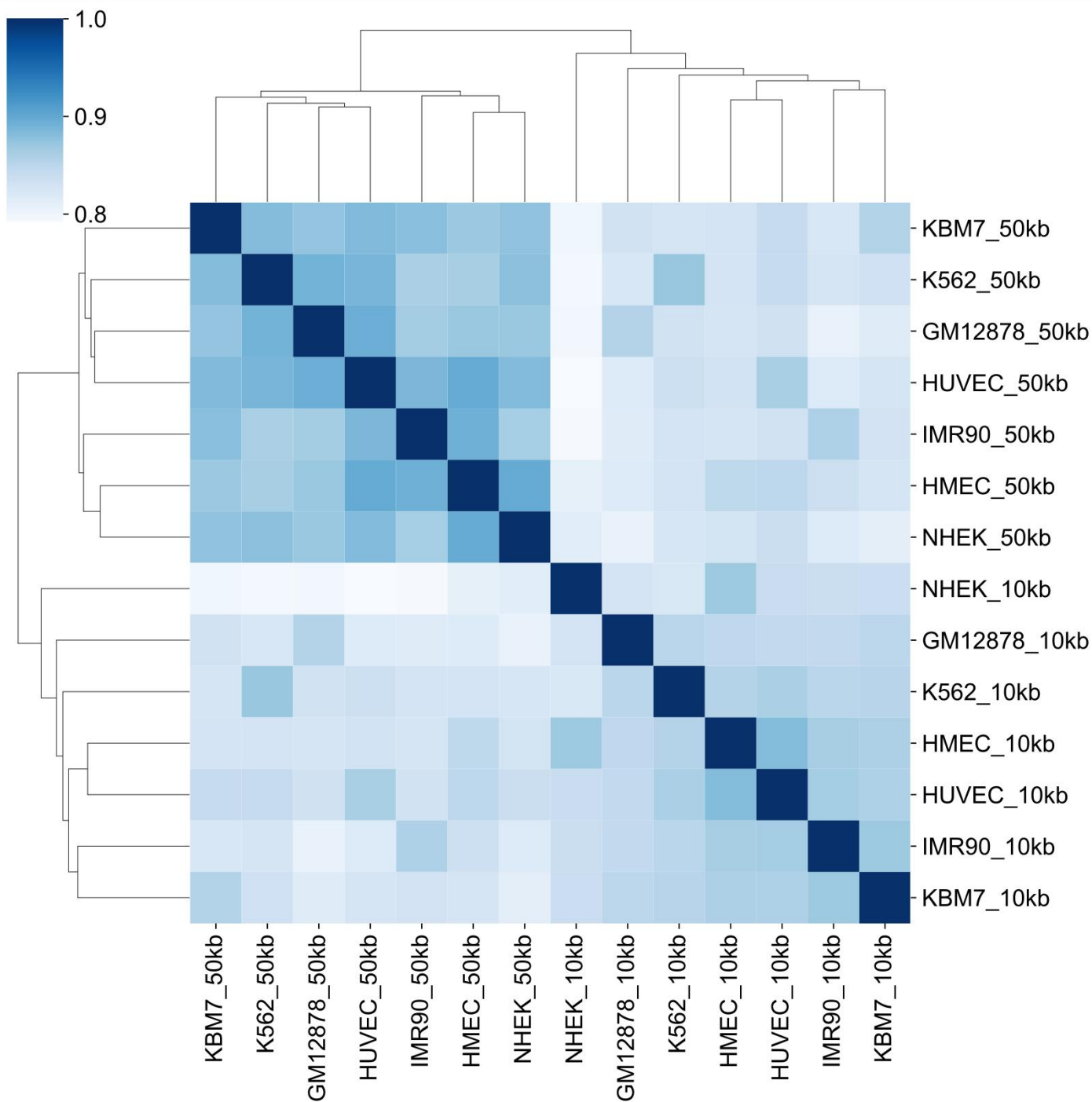
**e** Number of TAD boundary at each level

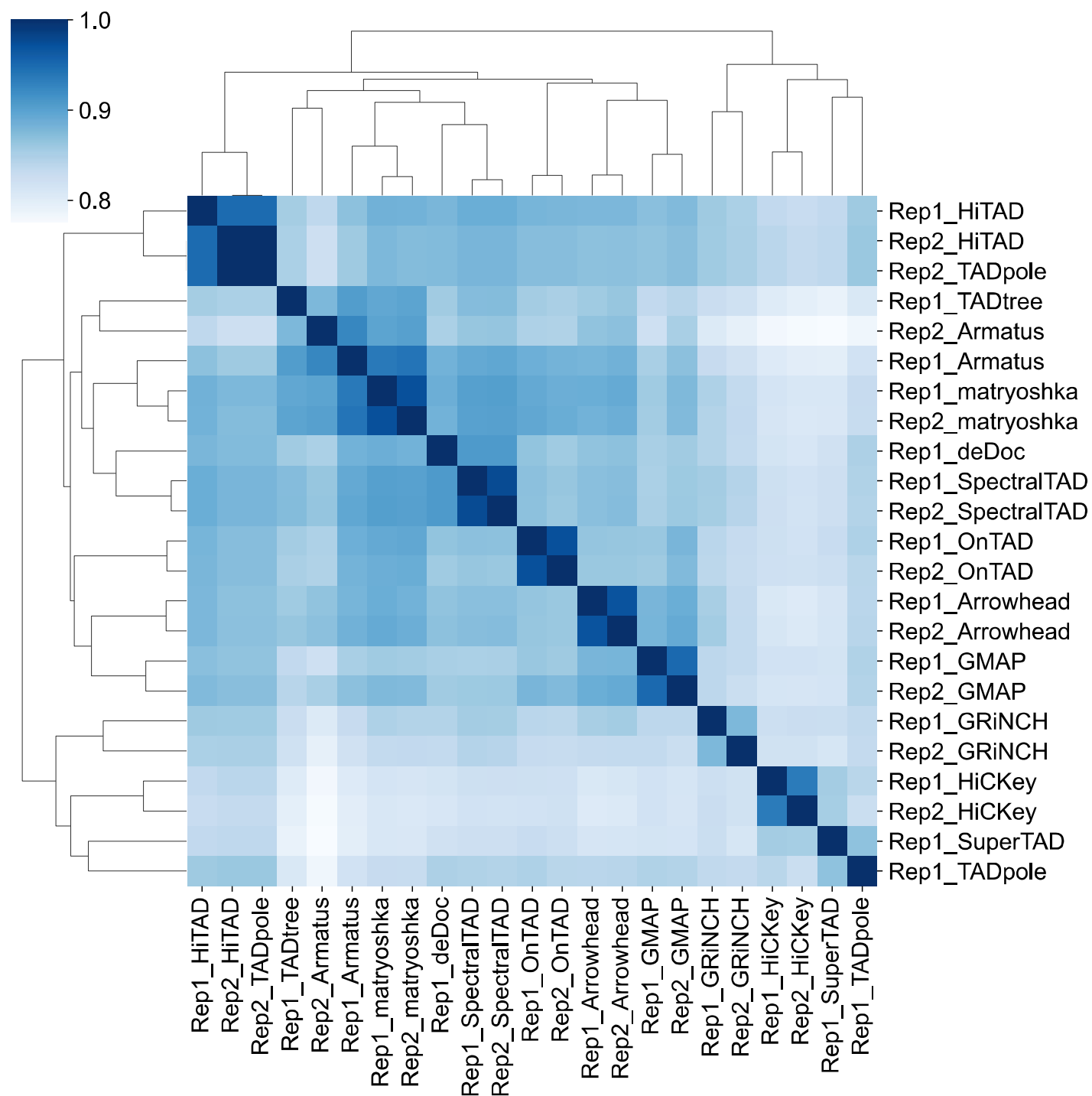


**f** Percent of TAD boundary at each level

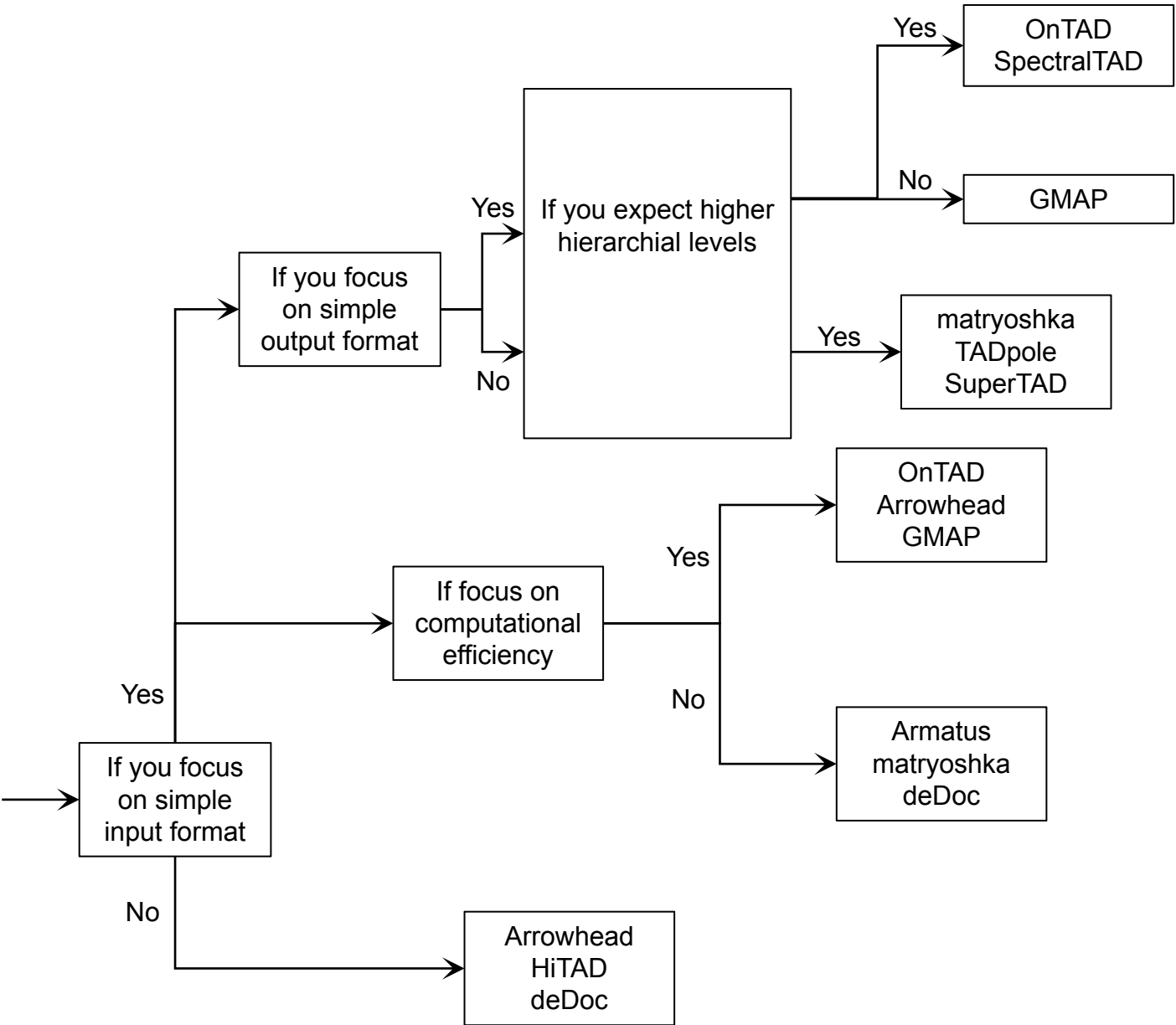


**Supplementary Figure 5. Hierarchical TADs in chromosome 7 of GM12878 from ICE-normalized Hi-C data.** (a) Ratios of TADs (a) and boundaries (b) at various levels of the GM12878 cell line on 10Kb. (c, d) Numbers (c) and ratios (d) of TADs at various levels of GM12878 cell line on 50Kb. (e, f) Numbers (e) and ratios (f) of boundaries at various levels of GM12878 cell line on 50Kb. Source data are provided as a Source Data file.

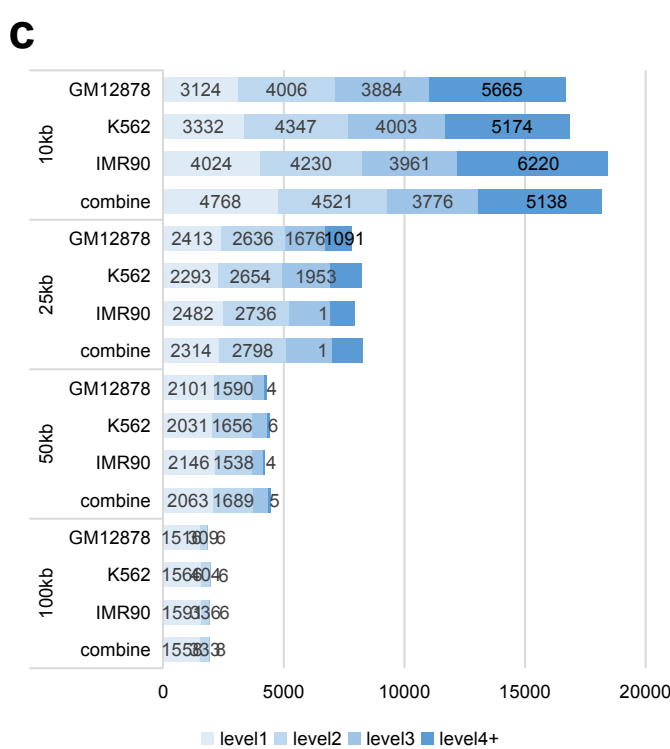
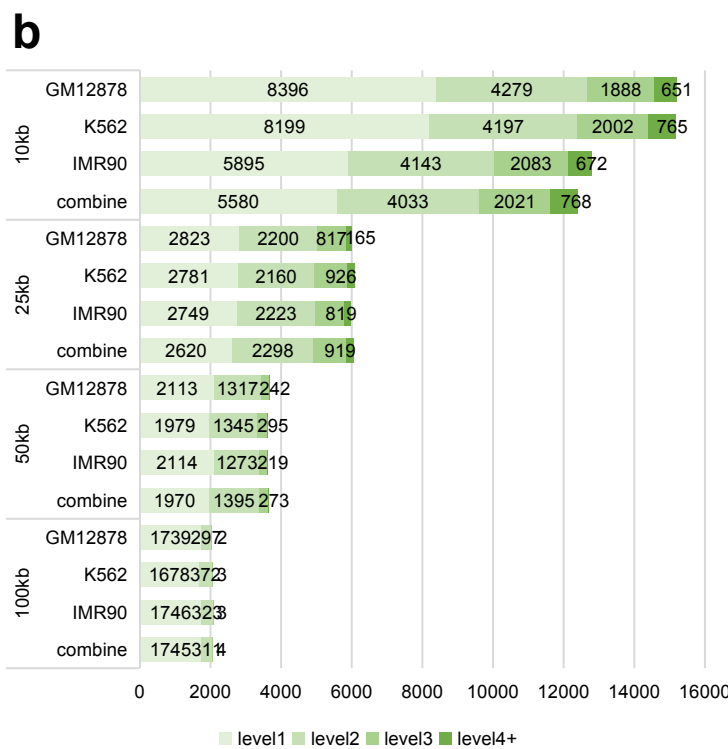
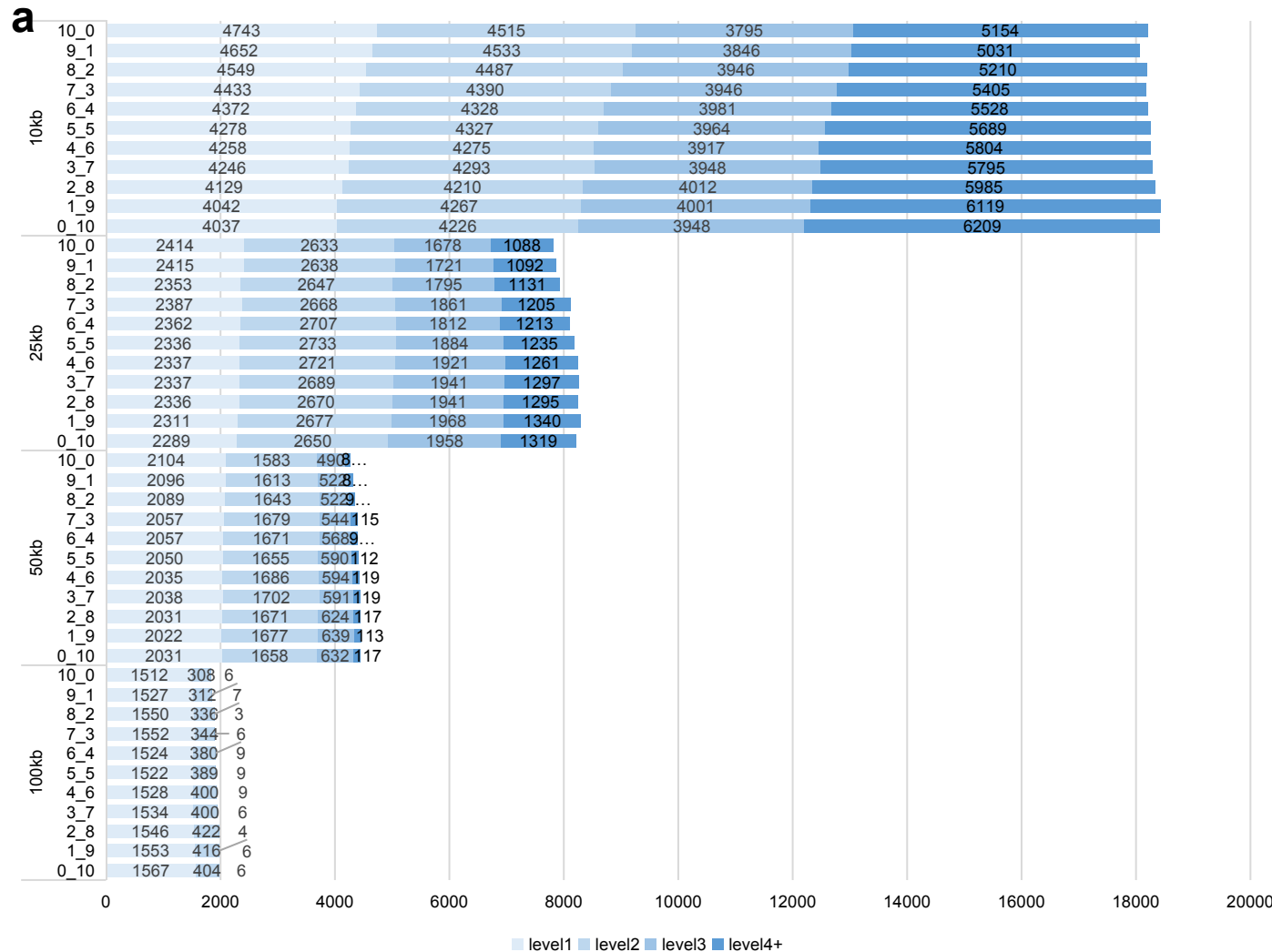
**a**

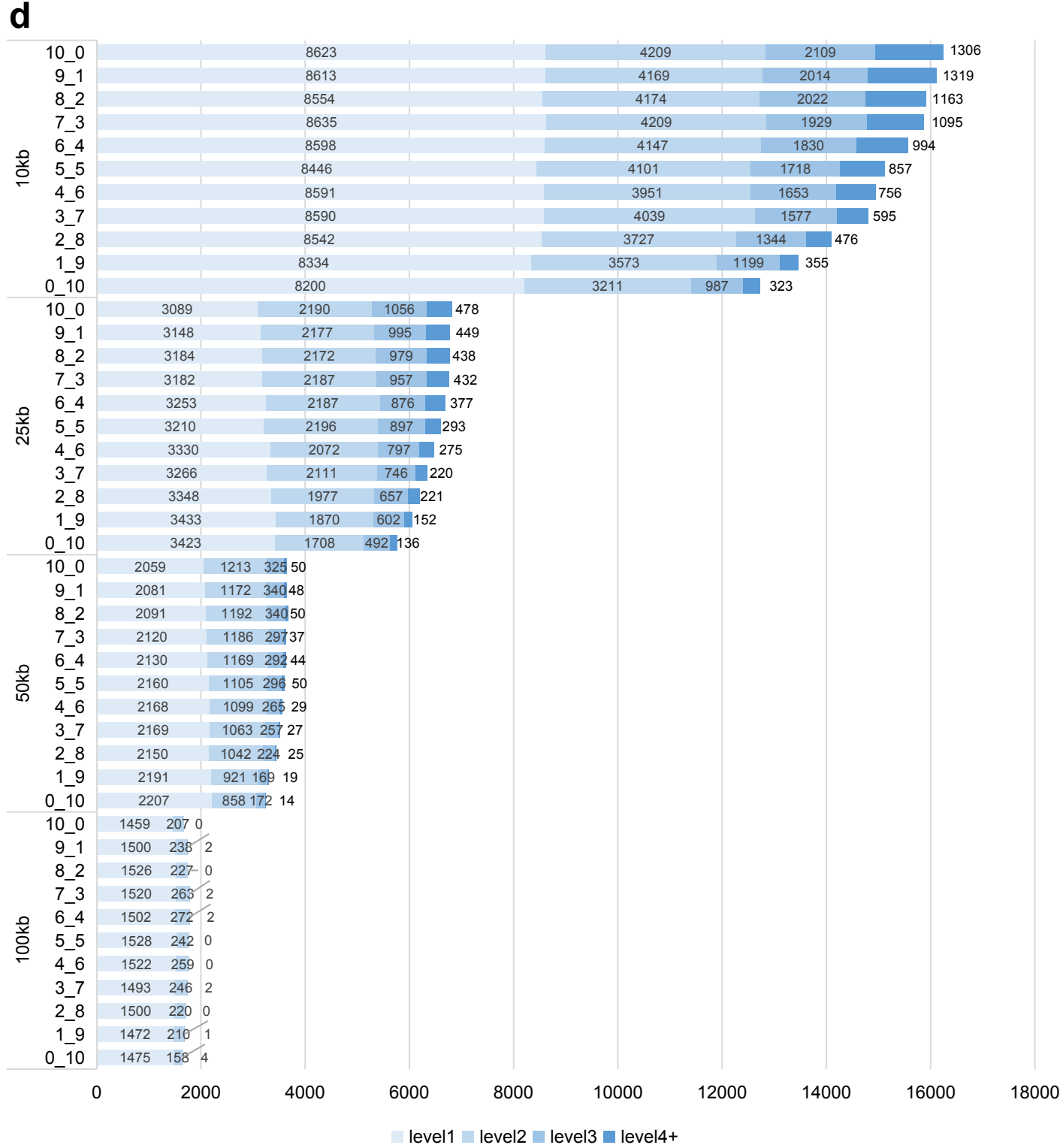
**b**

**Supplementary Figure 6. Hier\_SSIM among different resolutions, cell lines and biological replicates.** (a) Hier\_SSIM among TAD hierarchy obtained with 7 cell lines on 50Kb ICE data by OnTAD. (b) Hier\_SSIM among biological replicates in GM12878. Source data are provided as a Source Data file.



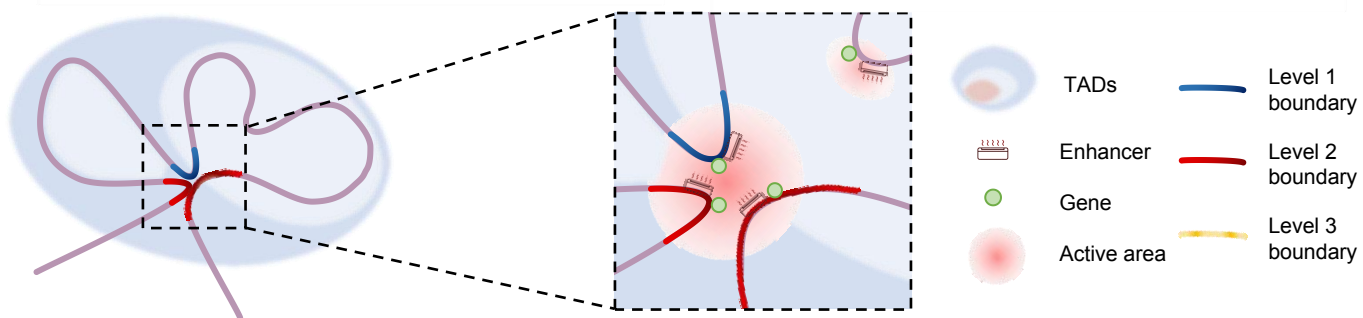
**Supplementary Figure 7. User-guidance for TAD hierarchy callers.**





**Supplementary Figure 8. TAD hierarchy of mixed samples.**

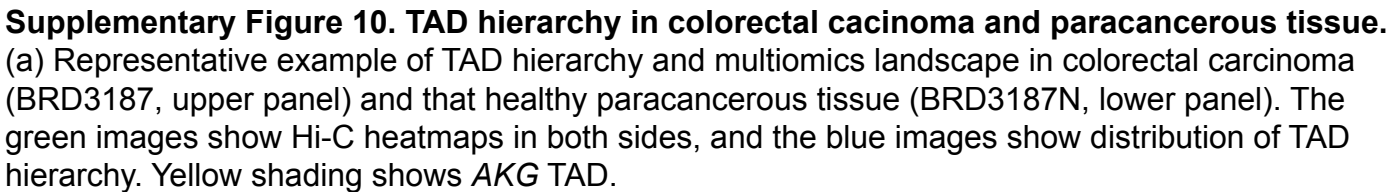
(a) Number of TADs at separate levels and various resolutions in mixed samples. (b, c) Number of boundaries (b) and TADs (c) at separate levels and various resolutions in GM12878 cell, K562 cell, IMR90 cell and mixed samples (from top to bottom). (d) Number of TADs at separate levels and various resolutions in Hi-C of mixed single cell samples.



## **Supplementary Figure 9. Histone modifications within TADs of all levels.**

(a) Enrichment of H3K4me1 (upper panel), H3K4me3 (middle panel), and H3K27me3 (lower panel) in TADs of level 1, 2, 3, and 4 plus.

(b) Representative example of TAD hierarchy and multiomics landscape in GM12878 cell (left panel) and K562 cell (right panel). The upper panels in both sides show distribution of Hi-C data. Areas with yellow and pink shading are selected to depict inter-cellular variation. (c) Schematic representation of the air conditioner model for TAD hierarchy.



## Supplementary Table 1

Overlap ratio between TAD hierarchy obtained at different resolutions in a pairwise measurement

|             | 5kb-10kb | 10kb-25kb | 5kb-25kb | 25kb-50kb | 10kb-50kb | 5kb-50kb | 50kb-100kb | 25kb-100kb | 10kb-100kb | 5kb-100kb |
|-------------|----------|-----------|----------|-----------|-----------|----------|------------|------------|------------|-----------|
| GRiNCH      | 0.726    | 0.738     | 0.713    | 0.739     | 0.704     | 0.699    | 0.728      | 0.719      | 0.683      | 0.657     |
| deDoc       | 0.698    | 0.759     | 0.620    | 0.780     | 0.710     | 0.580    | 0.815      | 0.725      | 0.659      | 0.525     |
| OnTAD       | 0.721    | 0.745     | 0.593    | 0.739     | 0.588     | 0.465    | 0.657      | 0.522      | 0.406      | 0.307     |
| Armatus     | 0.686    | 0.526     | 0.427    | 0.756     | 0.465     | 0.408    | 0.755      | 0.688      | 0.457      | 0.383     |
| GMAP        | 0.634    | 0.680     | 0.575    | 0.684     | 0.583     | 0.449    |            |            |            |           |
| matryoshka  | 0.581    | 0.635     | 0.616    | 0.664     | 0.608     | 0.501    | 0.592      | 0.576      | 0.551      | 0.512     |
| Arrowhead   | 0.572    | 0.654     | 0.419    | 0.686     | 0.534     | 0.351    | 0.411      | 0.286      | 0.204      | 0.174     |
| HiCKey      | 0.549    | 0.711     | 0.408    | 0.735     | 0.592     | 0.311    | 0.689      | 0.548      | 0.447      | 0.220     |
| SpectralTAD | 0.548    | 0.493     | 0.298    | 0.608     | 0.333     | 0.188    | 0.612      | 0.415      | 0.205      | 0.112     |
| SuperTAD    |          | 0.781     |          | 0.859     | 0.721     |          | 0.789      | 0.727      | 0.602      |           |
| HiTAD       | 0.840    |           |          |           | 0.649     | 0.621    |            |            |            |           |
| TADpole     |          |           |          | 0.848     |           |          | 0.885      | 0.792      |            |           |
| TADtree     |          |           |          |           |           |          | 0.697      |            |            |           |

## Supplementary Table 2

Ratio of Hier\_SSIM between 20% and 100% versus that between 50% and 100%

|             | 50kb  |       | 10kb  |       |
|-------------|-------|-------|-------|-------|
|             | 50%   | 20%   | 50%   | 20%   |
| TADpole     | 0.879 | 0.885 |       |       |
| SuperTAD    | 0.790 | 0.793 | 0.828 | 0.821 |
| deDoc       | 0.751 | 0.740 | 0.614 | 0.622 |
| HiCKey      | 0.736 | 0.734 | 0.742 | 0.743 |
| SpectralTAD | 0.731 | 0.721 | 0.684 | 0.684 |
| OnTAD       | 0.701 | 0.699 | 0.672 | 0.671 |
| GMAP        | 0.652 | 0.706 | 0.721 | 0.697 |
| HiTAD*      |       |       | 0.676 | 0.634 |
| GRiNCH      | 0.595 | 0.596 | 0.562 | 0.540 |
| TADtree     | 0.589 | 0.589 |       |       |
| matryoshka  | 0.509 | 0.512 | 0.418 | 0.521 |
| Armatus     | 0.496 | 0.452 | 0.518 | 0.481 |

\* The ratio of HiTAD equals Hier\_SSIM of 20% sample to Hier\_SSIM of 100% sample.

The cool inputs of 20% downsample are computed from sparse matrix by author, while those of 100% sample are cited from processed published cool files (<ftp://cooler.csail.mit.edu/coolers>).

### Supplementary Table 3

The running time and memory cost for each of 13 methods

|             |        | 100kb       | 50kb         | 25kb         | 10kb      | 5kb        |
|-------------|--------|-------------|--------------|--------------|-----------|------------|
| Arrowhead   | time   | 0m14.489s   | 0m24.141s    | 0m35.258s    | 1m6.845s  | 2m2.393s   |
|             | memory | 2.0G        | 3.9G         | 6.7G         | 9.9G      | 10.9G      |
| Armatus     | time   | 0m7.490s    | 0m22.973s    | 0m53.060s    | 6m48.109s | 32m58.254s |
|             | memory | 29.6M       | 116.9M       | 465.7M       | 2.8G      | 11.3G      |
| TADtree     | time   | 6m44.323s   | 62m27.921s   | 2274m51.231s |           |            |
|             | memory | 136.7M      | 371.1M       | 499.2M       |           |            |
| GMAP        | time   |             | ~20s         | ~1m          | ~3m       | ~10m       |
|             | memory |             | 1.2G         | 2.2G         | 18.0G     | 27.9G      |
| HiTAD       | time   | 10.579s     | 22.462s      | 53.770s      | 5m10.099s | 17m39.057s |
|             | memory | 598.8M      | 1.3G         | 1.6G         | 3.2G      | 4.4G       |
| deDoc       | time   | 0m22.88s    | 1m17.34s     | 4m18.36s     | 18m22.21s | 66m0.42s   |
|             | memory | 6.5G        | 12.3G        | 19.6G        | 26.7G     | 31.9G      |
| matryoshka  | time   | 0m7.117s    | 0m32.810s    | 2m35.674s    | 25m6.582s | 80m33.075s |
|             | memory | 39.5M       | 118.3M       | 465.8M       | 2.8G      | 11.3G      |
| OnTAD       | time   | 0m0.502s    | 0m1.342s     | 0m4.492s     | 0m27.758s | 1m59.385s  |
|             | memory | 53.9M       | 235.1M       | 1.8G         | 11.4G     | 45.5G      |
| TADpole     | time   | 46m53.274s  | 113m26.482s  | 257m9.550s   |           |            |
|             | memory | 927.7M      | 2.8G         | 5.1G         |           |            |
| SpectralTAD | time   | ~5s         | ~10s         | ~15s         | ~30s      | ~1m        |
|             | memory | 984.8M      | 1.2G         | 2.0G         | 6.10G     | 24.2G      |
| HiCKey      | time   | 0m0.653s    | 0m1.882s     | 0m4.289s     | 0m8.063s  | 0m11.179s  |
|             | memory | 39.5M       | 99.0M        | 139.2M       | 275.4M    | 433.8M     |
| SuperTAD    | time   | 917m48.012s | 8592m16.054s |              |           |            |
|             | memory | 11.2G       | 88.4G        |              |           |            |
| GRiNCH      | time   | 0m23s       | 0m48s        | 4m23s        | 10m22s    | 47m57s     |
|             | memory | 522M        | 1750M        | 6326M        | 37154M    | 145508M    |

The cells with slash main the computational limitation in resolution coverage of method or overloaded computing memory.