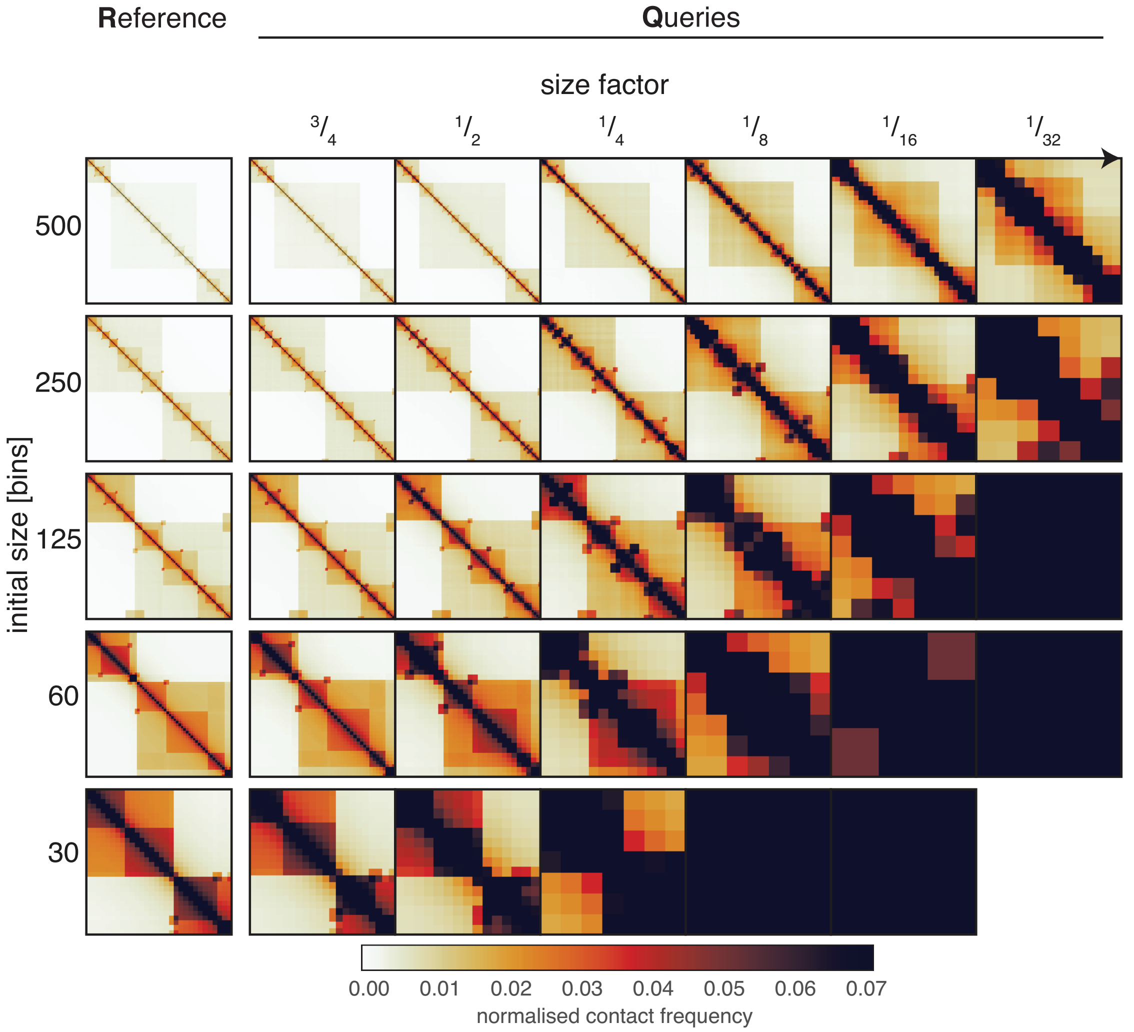
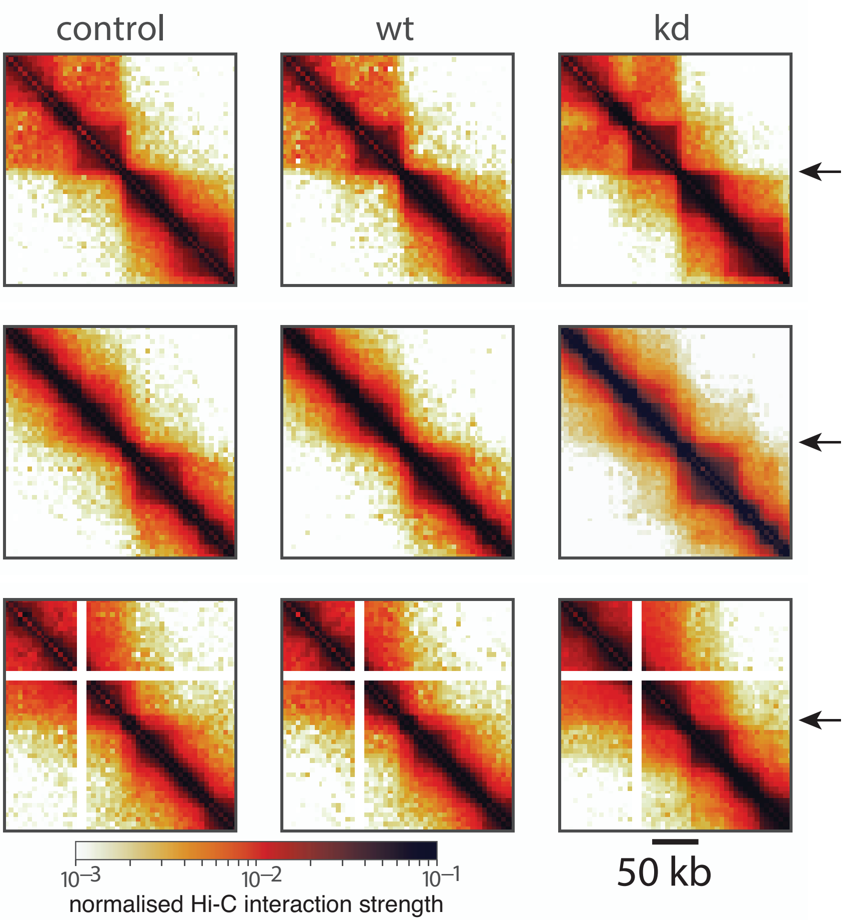
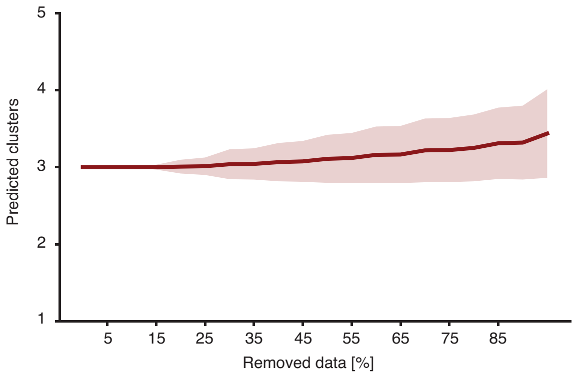


Supplementary Figure 1. Examples of synthetic matrices scaled to different sizes.

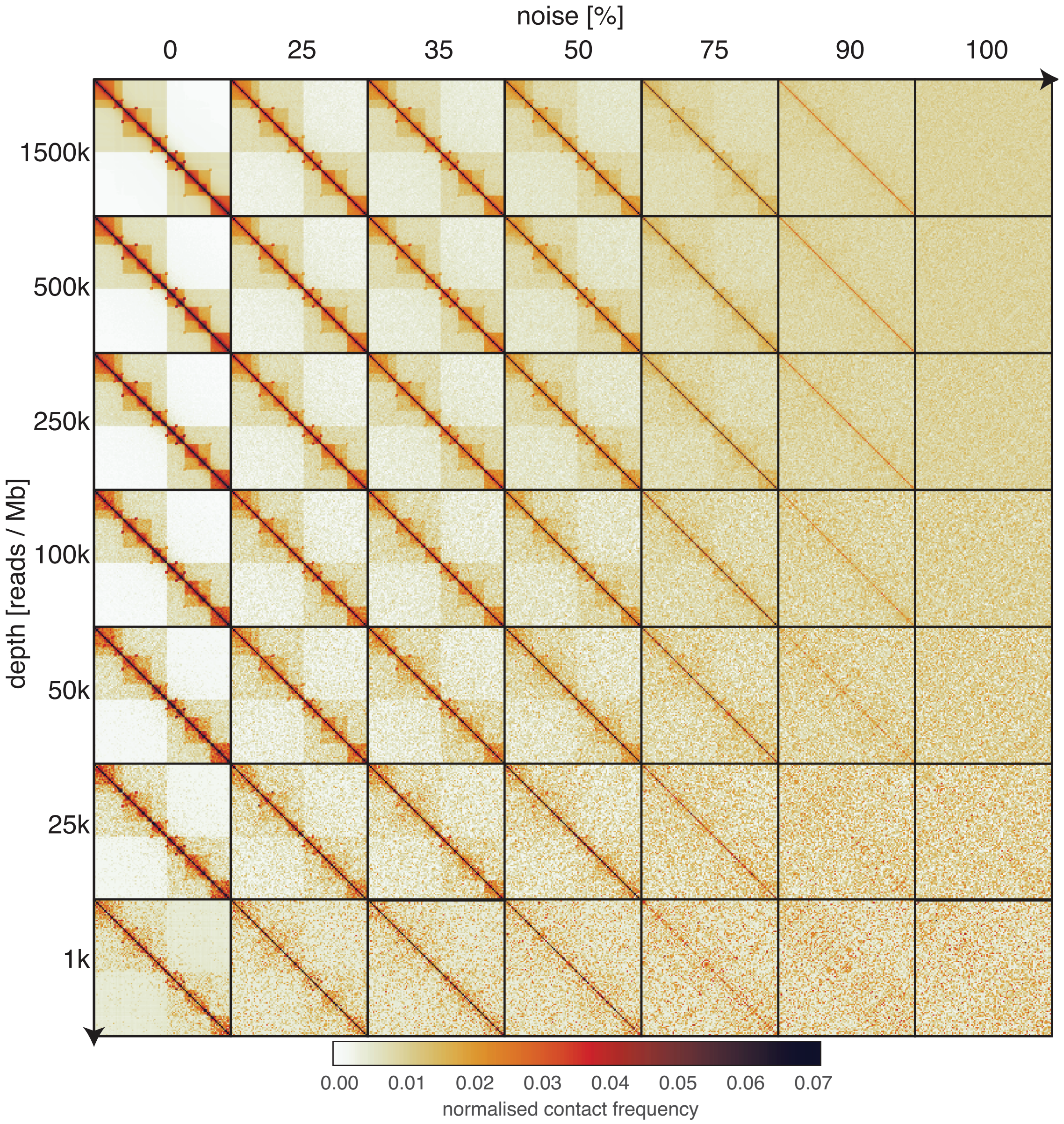
Matrix bins were rounded up to the nearest integer after scaling. Only matrices with at least two bins were plotted.



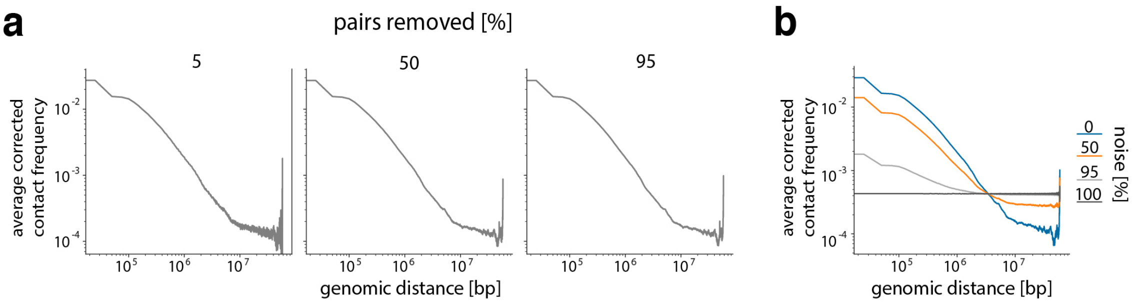
Supplementary Figure 2. Examples of minor changes in boundary strength after *zld* knockdown in *D. melanogaster*. Hi-C matrices are shown for a water injected control, wild type (wt) cells and cells after *zld* knockdown (kd). Arrows indicate positions of differential boundaries between wt and kd as identified previously[9]. White lines correspond to regions of the genome masked from the analysis due to low mappability.



Supplementary Figure 3. Effect of downsampling on number of optimal clusters. The optimal number of clusters was computed after downsampling all extracted features from the Hi-C data generated from healthy B-cells (control) and a diffuse large B-cell lymphoma (patient). This process was repeated 1,000 times. The solid line indicates the mean, shaded area corresponds to the standard deviation.



Supplementary Figure 4. Examples of synthetic matrices with varying levels of noise and simulated number of read pairs (depth). In all panels, depth was adjusted before adding noise.



Supplementary Figure 5. Effects of downsampling and noise on decay of average contact frequency with genomic distance. **a,** after downsampling to lower sequencing depths, **b,** with increased percentage of random ligations (= noise). Decay functions were computed on data from Bonev et al. 2017[12], on chromosome 19.