Methods

Insulation index

The raw insulation index is calculated as in Crane *et al.* (2015), by summing up values in a square region in a Hi-C plot with a certain width (window size), starting from the diagonal. To call TADs, we first identify potential TAD boundaries as zero-crossings of the first derivative of the insulation index, where the second derivative is positive (valleys in the insulation index plot). For a boundary to be considered a "true" boundary, we require the absolute value of its insulation index to be below a user-defined cutoff. We call a TAD a region in-between two true boundaries where the insulation index is higher than the user-defined cutoff for least one point in the region.

Directionality index

The raw directionality index is calculated as in Dixon *et al.* (2012),

$$DI = \left(\frac{B-A}{|B-A|}\right)\left(\frac{(A-E)^2}{E} + \frac{(B-E)^2}{E}\right)$$

where A and B are number of reads that map to a bin upstream and downstream in the Hi-C matrix, respectively, within a given window size, and E is the expected number of reads under the null hypothesis, $E = (A+B)/2$.

In contrast to the original authors, we do not apply a Hidden Markov Model to identify the "true" directionality bias of any given region, as the added complexity does not allow efficient on-the-fly computation of TADs in an interactive environment.

We call a region a TAD, if it is framed by a bin with a strong downstream directionality bias at the 5', and a bin with a strong upstream directionality bias at the 3'

end. A “strong” bias is defined as a directionality index that crosses a user-defined threshold.

References

Crane,E. *et al.* (2015) Condensin-driven remodelling of X chromosome topology during dosage compensation. *Nature*, **523**, 240–244.

Dixon,J.R. *et al.* (2012) Topological domains in mammalian genomes identified by analysis of chromatin interactions. *Nature*, **485**, 376–80.