# Spatio-temporal organisation of replication
# Part II : Relation to open chromatin encoded in DNA sequence

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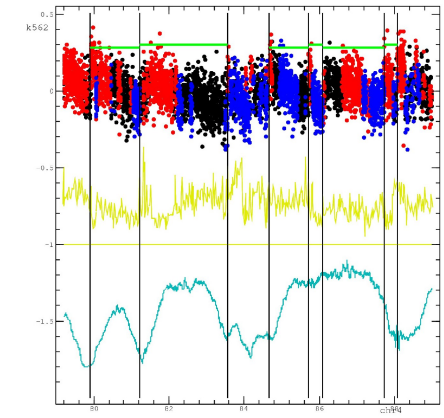
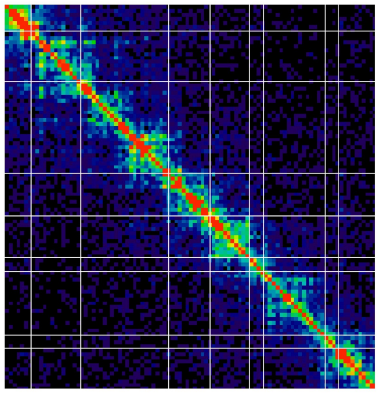
In this second talk, we will focus on the relationship between replication N-domains and the functional and structural organisation of the genome. Analysing the distribution of genes along N-domains, we show that genes with a CpG rich promoter are more abundant at N-domain borders and that, close to these putative replication origins, transcription is mainly co-oriented with replication. We observe that regions a ~200 kilobase-pair wide surrounding most of these origins are hypersensitive to DNase I cleavage, are hypomethylated and present a significant enrichment in genomic energy barriers that impair nucleosome formation (nucleosome free regions). Hence, putative replication origins are likely specified by an open chromatin fibre structure favoured by the DNA sequence. Interestingly, we also observe a high evolutionary breakpoint density in these open chromatin regions, suggesting that susceptibility to breakage might be linked to local open chromatin fibre state. Finally, we explore the relationship between N-domains and large-scale chromatin conformation using recently published Hi-C data.

In conclusion, we will emphasize the set of putative replication initiation zones at the border of N-domains as a peculiar subclass of origins central to the coordination of the spatio-temporal replication programme. These "master" origins are at the heart of a remarkable organisation of the human genome, which integrates transcription, replication and chromatin structure as co-ordinated determinants of genome architecture and evolution.



(TOP) Compositional asymmetry along a fragment of chromosome 4; dot colors correspond to intergene (black), sense (red) and anti-sense (blue) genes. Yellow curve correspond to GC content and blue curve to timing profile for K562 cell line (data from Hansen *et al.*, PNAS 107 (2010)). N-domains are shown as green bars; vertical lines mark their borders.
(BOTTOM) Matrix of Hi-C chromosome interaction count at 100kbp resolution (data from Lieberman-Aiden *et al.*, Science 326 (2009)). White lines mark N-domains borders.

Audit *et al.*, Open chromatin encoded in DNA sequence is the signature of 'master' replication origins in human cells. *Nucleic Acids Reseach* 37, 6064 (2009).
Audit *et al.*, DNA Replication timing data corroborate in silico human replication origin predictions. *Physical Review Letters* 99, 248102 (2007)