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Navigation and target search on human chromosomes

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In living cells, proteins often bind to specific basepair sequences on DNA, such as transcription factor proteins that regulate gene expression, or restriction enzymes that cut the DNA at cleavage sites. These proteins search for targets that are about 10 basepairs long, on a DNA that is a few mega basepairs in bacteria, and billions in humans. This sounds like a needle in a haystack- problem but search times are surprisingly short. For example, in *E. coli* bacteria it takes a few minutes to locate a gene regulatory site, whereas a random search would take up to ten times longer. The common explanation for this, is that proteins combine three dimensional (3D) excursions with one dimensional (1D) diffusion along the DNA, also known as facilitated diffusion.

Combining 3D and 1D search in this way implies that search times depend on the DNA's specific 3D organisation. This has been shown analytically using classical polymer models with known looping probabilities and in simulations. But, how this happens in humans and other eucaryotes where DNA organisation is more complex is an open problem. Theoretically, researchers have been hampered by the lack of knowledge of how eukaryotic DNA is organised, but experimental development of so-called Chromosome Conformation Capture techniques, where state-of-the-art is HiC, have partly remedied this problem. In short, HiC experiments give a genome-wide heat map of physical contact frequencies, or looping probabilities, between all DNA fragments pairs in the cell nucleus down to 1 kilo-basepair resolution.

In our recent work, we have used HiC data as a proxy for the *in-vivo* DNA looping probabilities to model protein search on human chromosomes. By mapping the search onto a network problem, with DNA segments as nodes and physical contacts as links, we calculate the mean-first passage time to all nodes for all human chromosomes. For example, we find that DNA segments that harbour gene starts have small search times and are thus easy to find.

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