Road signs and traffic signals on DNA: Physical model describes the distribution of nucleosomes

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The DNA genomes of organisms whose cells possess nuclei are packaged in a highly characteristic fashion. Most of the DNA is tightly wrapped around protein particles called nucleosomes, which are connected to each other by flexible DNA segments, like pearls on a necklace. This arrangement plays a major role in deciding which genes are actively expressed, and thus which proteins can be synthesized in a given cell.

The biophysicists Professor Ulrich Gerland and Wolfram Moebius from Ludwig-Maximilians-Universitaet (LMU) in Munich have recently developed a model which explains the distribution of nucleosomes around the functionally crucial transcription start sites. Transcription is the first step in the process that converts genetic information into proteins. At the transcription start sites the DNA must be free of nucleosomes.

The two researchers discovered that distinct stop signals positioned on either side of these zones must actively prevent the formation and sliding of nucleosomes. "Our model provides a useful tool for dissecting the so-called chromatin code, which determines how the DNA is packed and selectively made accessible for transcription", says Gerland. (*PLoS* Computational Biology, 19 August 2010)

In higher organisms, the genetic material in each cell is packed in the

form of compact chromosomes in the nucleus. The basic structural unit of a chromosome is the nucleosome. The nucleosomes, each made up of two copies of four different histone proteins, provide a kind of spool on which the DNA strands are wound, and are linked together by more flexible sections of DNA, like beads on a string. But nucleosomes are not just passive packages that keep the DNA in a compact form. "They have a decisive influence on gene regulation, insofar as they help to control which segments of the DNA can be translated into proteins", explains Gerland, Arnold Sommerfeld Center for Theoretical Physics (ASC) and Center for NanoScience (CeNS) in the Physics Faculty of LMU Munich.

The accessibility of the DNA is a primary determinant of gene expression, and is therefore of great interest to molecular geneticists. A central question is how nucleosomes are distributed around the regions at which transcription starts. The selection of the start site, or gene promoter, is the first crucial step in the conversion of genetic information into the bricks and mortar of all cells, the proteins. It turns out that these promoter sites are marked by the presence of a nucleosome-free zone flanked by a specific pattern of nucleosomes. The biological function of these gaps seems to be to provide accessible docking sites for the transcriptional machinery, which comprises a multiprotein complex consisting of many subunits.

Together with his PhD student Wolfram Moebius, Gerland has asked whether a simple physical principle might not account for the characteristic distribution of nucleosomes in the vicinity of transcription start sites. The researchers made use of the so-called Tonks model, which applies to interactions between diffusing particles that are confined to one dimension. "Provided one knows the position of a single particle, one can use the model to predict, in a statistical sense, the positions of the particles in the vicinity" ", says Wolfram Moebius, who is the first author on the new study. "In addition, one observes a typical

pattern of oscillations in the particle density." The analyses showed that the model of a Tonks gas indeed describes the distribution of the nucleosomes with surprising precision.

"When we plug average values derived from a large set of promoter regions into the model, the calculations reproduce the typical range of variation in nucleosome density that we see in biological systems", explains Gerland. The new model agrees best with the biological data if one assumes that the boundaries on either side of a nucleosome-free zone are defined by different conditions. "On the side nearer the transcription initiation site, there must be a fixed nucleosome that prevents sliding along the DNA, like a sign saying 'Road Closed'", explains Gerland. "At the other end of the open stretch there has to be a larger segment that is refractory to nucleosome assembly. In other words, there must be a signal that serves as a No Parking sign for nucleosomes."

The results obtained by Möbius and Gerland for the first time quantitatively confirm a statistical model for the distribution of nucleosomes in the genome proposed by the American biochemist Roger Kornberg, (who first discovered nucelosomes in 1974, and won the Nobel Prize for Medicine for his studies on the structure of RNA polymerase in 2009). The new model contributes to our understanding of the rules that determine how chromosome structure is established and modulated. "Our calculations should certainly help to decode the so-called chromatin code, the basis for which is not well understood", says Gerland. "This code provides the blueprint for the three-dimensional structure of the genome."

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