Errant gliding proteins yield long-sought insight

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In order to react effectively to changes in the surroundings, bacteria must be able to quickly turn specific genes on or off. Although the overall mechanisms behind gene regulation have long been known, the fine details have eluded scientists for decades. Researchers at Uppsala University can now provide a picture of how proteins regulate genetic expression at the atomic level.

Genes can be regarded as blueprints for all of the molecular machines —normally proteins—that perform the tasks an organism needs for survival. Under different living conditions, different types of proteins are needed to break down the available types of nutrients, for example.

Because the surroundings can change rapidly, it is also important for bacteria and other organisms to be able to quickly reconfigure their biochemical operations in order to adapt to the new environment. This is done through regulation of the activity of proteins that already exist in the cell, but also by the binding of special proteins—transcription factors —to specific sites on the DNA, turning certain genes on or off, which in turn regulates the cell's production of various proteins.

"The latter might seem impossible, as an arbitrary transcription factor normally exists in just a handful of copies inside a bacterial cell, and one of them has to find a specific binding site on the DNA spiral, which contains some five million base pairs, in order to turn a gene on or off," says Erik Marklund, one of the lead authors of the new study.

Roughly 40 years ago it was observed that these transcription factors find their binding sites on DNA much more quickly that free diffusion in three dimensions would allow. Theoretical and empirical studies have shown that it is likely that the transcription factors bind to a chromosome wherever they encounter one and then glide along the DNA in search of their binding sites. This enables a dramatically faster search process, but precisely how this happens has been obscure, until now.

Using large-scale computer simulations, researchers in Johan Elf's research team at Science for Life Laboratory at Uppsala University managed to study in detail how the transcription factor LacI moves along DNA in a spiral path. The study, to be published in a coming issue of *Proceedings of the National Academy of Sciences* (*PNAS*), compares the energy required to break off the interaction with DNA with the energy needed to glide along the DNA and how many times a protein binds back to the same DNA strand before it starts to look elsewhere. From this comparison, the scientists derived the average time the transcription factor is bound to the DNA and how much of the DNA it has time to search through before it lets go.

"The insights from the study are of the greatest significance for our understanding of how the activity of genes is regulated. Not least they indicate how various DNA-binding proteins affect each other by acting as 'roadblocks' that impede the process. Ultimately this new knowledge also provides guidance regarding how the activity of genes can be manipulated."

Enhancing our understanding of how molecular interactions at the atomic level have consequences for the genetic activity of a cell brings new avenues for medical research. For example, improved simulation methods make it possible to test how new drugs can be expected to impact cells before they are even produced and tested in reality.

More information: Transcription-factor binding and sliding on DNA studied using micro- and macroscopic models, www.pnas.org/cgi/doi/10.1073/pnas.1307905110

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