Steps that lead to genes being switched on revealed in atomic simulation

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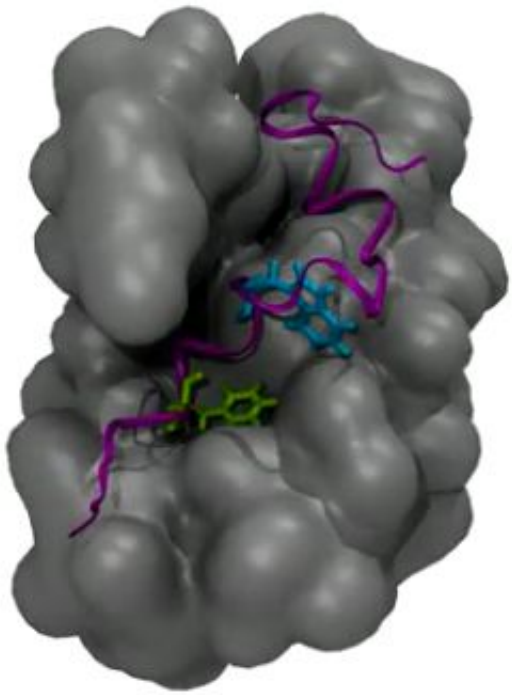

Proteins are essential for processes that sustain life. They are created in cells through a process called gene expression, which uses instructions from stretches of DNA called genes to build proteins. Sometimes genes are faulty and create proteins that contain errors, preventing the cell from functioning properly. These lead to genetic diseases like cystic fibrosis and haemophilia.

Gene expression is controlled by molecules called transcription factors, which bind to the start of a gene sequence at its 'basal machinery' and tell it to switch on and start creating certain proteins.

The way transcription factors bind to the basal machinery is a 'fuzzy' process, meaning the exact sequence of events is unknown because the steps do not exist for long enough to be captured by traditional imaging techniques.

But now, by creating a computer simulation of all of the tens of thousands of atoms making up the process and modelling their movements in 50 million separate steps, researchers at Imperial College London have been able to determine the sequence of events that lead to genes being switched on.

The simulated process revealed 'pockets' in the gene basal machinery, which the transcription factors move in and out of during binding. Knowing how these structures fit together could lead to the design of molecules that interfere with or disrupt the process, potentially tackling diseases.

Lead researcher Dr Robert Weinzierl from Imperial's Department of Life Sciences said: "For the first time, we can fill in the dynamic landscape of interaction between transcription factors and basal machinery. This is a central mechanism for gene expression - the interactions here determine whether a gene gets switched on and creates proteins."

"Gene regulation is a completely new drug target that has previously been too challenging to explore," added Dr Weinzierl. "This process influences biology on a really fundamental level, and could allow us to prevent the expression of detrimental genes."

The researchers' new technique predicts the movements of all the atoms in order to build up a picture of the structures involved changing every couple of femtoseconds - quadrillionths of a second. The results of the first trial of the technique are reported today in *PLOS Computational Biology*.

Dr Weinzierl has submitted a patent application for his computer-based approach to studying gene expression interactions. Using this, compounds could be screened for possible fit into the basal machinery pockets.

"With computer simulation, it becomes easy to identify candidate compounds that could target these interactions without the need to test them first in real life, cutting down the time required to sift for new drugs," said Dr Weinzierl.

More information: 'Molecular Dynamics of "Fuzzy" Transcriptional Activator-Coactivator Interactions' by R Weinzierl and N Scholes, 13 May 2016, *PLOS Computational Biology*. journals.plos.org/ploscompbiol … al.pcbi.pcbi.1004935

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