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Simulating Protein-DNA Switches

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Perhaps the single most important component of many biological control networks is the switching of transcription by control (C) proteins that complex specifically to promoter DNA sequences in order to activate or repress transcription. Whereas the repression mechanism is quite easily visualized (the repressor protein blocks access of the RNA polymerase to the promoter sequence and therefore blocks transcription of the encoded gene), activation is more difficult to understand. Binding an activating C-protein must recruit the sigma-subunit of the RNA-polymerase to bind to the promoter region of the DNA. We will address two aspects of these switching mechanisms; how do repressor proteins that are themselves switched by small molecules or peptides achieve this switching and how does an activator protein recruit the sigma subunit? The latter question is closely interlinked with that of how C-proteins achieve their high selectivity for specific DNA sequences. We will discuss very extensive molecular dynamics (MD) simulations on TetR, a repressor protein that is switched by tetracycline antibiotics, and the finely tuned Esp1396I bacterial restriction-modification (RM) system. The latter is particularly interesting because the same C-protein acts as promoter and repressor, depending on its concentration. The result is a temporal control of the RM system that is essential for it to function correctly. Our results will emphasize the role of MD simulations as prospective research tools in this area, but will also point out their limitations and the need for exhaustive validation.