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Stochastic search in gene regulation in and ex vivo: Levy flights and weak ergodicity breaking

Gene regulation rests on certain regulatory proteins searching megabases along a DNA molecule for their specific binding site, in order to recruit the biochemical machinery of the cell for reading out the local genetic code. Most experimental data come from in vitro conditions in a dilute solution with only few protein species.

Under such dilute conditions it was shown that a combination of different Brownian search mechanisms reproduces the measured search rates. In particular, the search is performed by bulk diffusion in combination with one-dimensional diffusion of the protein along the DNA mediated by nonspecific binding. I will discuss the third mechanism, namely, intersegmental transfers: the protein can bridge from one segment of the DNA to another, in cases when the DNA loops back on itself, due to its polymeric nature. Approximately, this gives rise to a Levy flight in the chemical coordinate of the DNA, a process that is shown to further optimize the search.

In vivo, however, the cell is superdensely packed with large molecules, such as proteins, ribosomes, RNA, etc. This causes the effect of "molecular crowding" that, in turn, gives rise to subdiffusion of larger biomolecules. I will show that this changes the behaviour of the search process significantly, including effects of weak ergodicity breaking. The latter would allow the cell to combine high accuracy of gene regulation with low numbers of regulatory proteins.

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