# Search for a small target in biological cells: the necessity to go beyond mean rates

by D. S. Grebenkov, R. Metzler, and G. Oshanin

Email: denis.grebenkov@polytechnique.edu

The first-passage time (FPT), i.e., the moment when a stochastic process reaches a given threshold value for the first time, is a fundamental mathematical concept with immediate applications. In particular, it quantifies the statistics of instances when biomolecules in a biological cell reach their specific binding sites and trigger cellular regulation. Typically, the first-passage properties are given in terms of mean first-passage times. However, modern experiments monitor single-molecular binding-processes in living cells and thus provide access to the full statistics of the underlying first passage events, in particular, inherent cell-to-cell fluctuations. We here present a robust explicit approach for obtaining the distribution of FPTs to a small target region in cylindrical-annulus domains, which represent typical bacterial and neuronal cell shapes. We investigate various asymptotic behaviors of this FPT distribution and show that it typically is very broad in many biological situations: thus, the mean FPT can differ from the most probable FPT by orders of magnitude. The most probable FPT is shown to strongly depend on the starting position within the geometry and to be almost independent of the target size and reactivity. These findings demonstrate the dramatic relevance of knowing the full distribution of FPTs and thus open new perspectives for a more reliable description of many intracellular processes initiated by the arrival of one or few biomolecules to a small, spatially localized region inside the cell.