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Rad4 recognition-at-a-distance: Physical basis of conformation-specific anomalous diffusion of DNA repair proteins

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ABSTRACT

Since Robert Brown's first observations of random walks by pollen particles suspended in solution, the concept of diffusion has been subject to countless theoretical and experimental studies in diverse fields from finance and social sciences, to physics and biology. Diffusive transport of macromolecules in cells is intimately linked to essential cellular functions including nutrient uptake, signal transduction, gene expression, as well as DNA replication and repair. Advancement in experimental techniques has allowed precise measurements of these diffusion processes. Mathematical and physical descriptions and computer simulations have been applied to model complicated biological systems in which anomalous diffusion, in addition to simple Brownian motion, was observed. The purpose of this review is to provide an overview of the major physical models of anomalous diffusion and corresponding experimental evidence on the target search problem faced by DNA-binding proteins, with an emphasis on DNA repair proteins and the role of anomalous diffusion in DNA target recognition.

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Diffusive transport lies at the heart of a broad array of cellular processes. A specific topic of interest is how proteins perform diffusion, either one- or three-dimensional, in search of their targets in DNA. Such targets may be a particular DNA sequence in the case of a transcription factor, or a damaged base in the case of a DNA repair enzyme. We preface these discussions by briefly introducing the diffusive process with a historical perspective. To exemplify the target search process, we consider the case of the DNA repair heterodimer Rad4-Rad23, the yeast homolog of human XPC-HR23B that is involved in the initial damage recognition step in nucleotide excision repair, which performs anomalous diffusion on DNA containing UV-induced photoproducts. This is followed by an overview of several well-established physical models and corresponding experimental observations of anomalous diffusion, particularly subdiffusion. We then focus our attention specifically on the diffusive search problem for DNA-binding proteins with cognate target sequences. Finally, we close by discussing working models for one-dimensional apparent anomalous diffusion by proteins in target search on DNA and the broader implications for biological functions.

1. Introduction to diffusion

1.1. Brownian motion

When observing pollen particles from the plant *Clarkia pulchella*, suspended in solution, through his single lens microscope in June of 1827, Scottish botanist Robert Brown noted their peculiar random jiggling motion (Brown, 1828). He went on to discover the same property of microscopic particles suspended in liquids in other pollen grains, powders of fossil wood, window glass, minerals, rocks, and even a fragment of the Sphinx (Brown, 1828). In a follow up publication, Brown reiterated that such perplexing motion was exhibited by "extremely minute particles of solid matter, whether obtained from organic or inorganic substances, when suspended in pure water, or in some other aqueous fluids," and that it did not arise from currents in the fluid or as a result of evaporation (Brown, 1829). The random walk of microscopic particles in suspension has since been termed Brownian motion (Fig. 1A) in honor of Robert Brown.

1.2. Fickian diffusion

The first quantitative phenomenological description of macroscopic diffusion was developed by physiologist Adolf Fick in 1855, based on the idea of macroscopic concentrations and fluxes (Fick, 1855). Inspired by Fourier's law of heat conduction and Ohm's work on electric conductivity, Fick's first law proposes that the one-dimensional flux is inversely proportional to the concentration gradient:

$$j = -D\frac{\partial c}{\partial x} \tag{1}$$

where j is the flux in the units of number per unit area per unit time, c the concentration of particles in the units of number per unit volume, x in the units of length, and D the diffusion coefficient in the units of $length^2/time$. By invoking conservation of mass in combination with Fick's first law and the assumption that the diffusion coefficient D is a constant, we arrive at the law of diffusion in one dimension, or Fick's second law:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial^2 x} \tag{2}$$

Consider the case $c(x,t)$ where there the initial concentration at $t = 0$ is a spike at $x = 0$, or

$$c(x,0) = N\delta(x) \tag{3}$$

where $\delta(x)$ is the Dirac delta function (Phillips et al., 2009). The solution to Fick's second law then takes the form

$$c(x,t) = \frac{N}{\sqrt{4\pi Dt}}e^{\frac{-x^2}{4Dt}} \tag{4}$$

i.e. a zero-mean Gaussian distribution that broadens over time

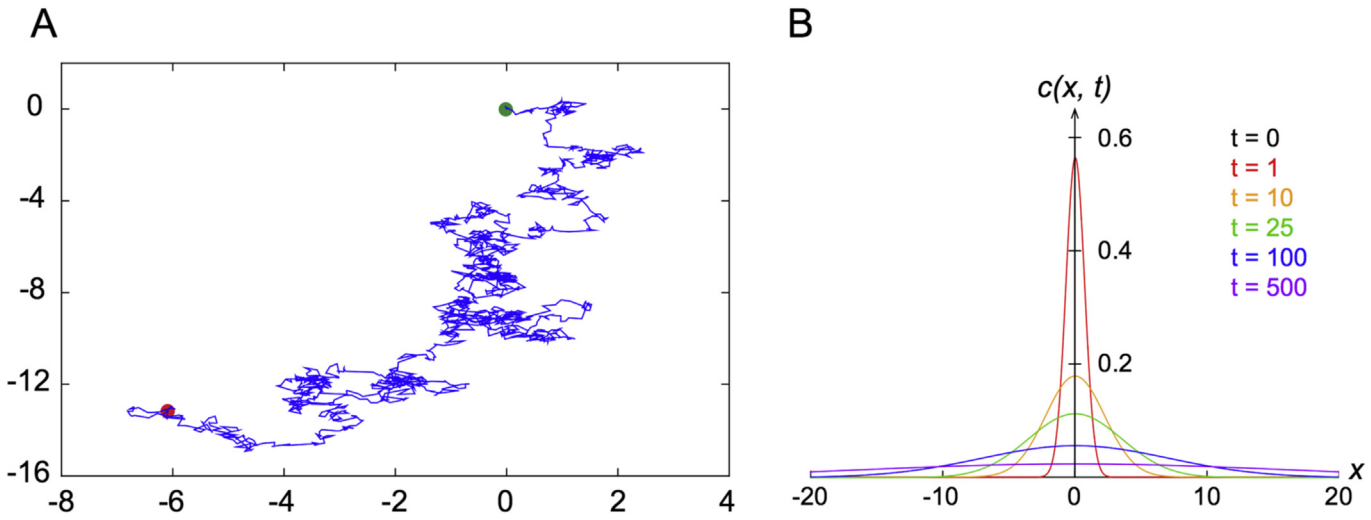

Fig. 1. Random Walk and Diffusion.
A. Simulated two-dimensional Brownian motion. Green and red dots indicate the start and end of the trajectory, respectively.
B. Plot of the time evolution of the solution $c(x,t)$ Eq. (4) to a one-dimensional Fickian diffusion that starts as a point source at the origin.