

# Time and space generalized diffusion equation on graph/networks

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Normal and anomalous diffusion are ubiquitous in many complex systems [1]. Here, we define a time and space generalized diffusion equation (GDE), which uses fractional-time derivatives and transformed  $d$ -path Laplacian operators on graphs/networks. We find analytically the solution of this equation and prove that it covers the regimes of normal, sub- and superdiffusion as a function of the two parameters of the model. We extend the GDE to consider a system with temporal alternancy of normal and anomalous diffusion which can be observed for instance in the diffusion of proteins along a DNA chain. We perform computational experiments on a one-dimensional system emulating a linear DNA chain. It is shown that a subdiffusive-superdiffusive alternant regime allows the diffusive particle to explore more slowly small regions of the chain with a faster global exploration, than a subdiffusive-subdiffusive regime. Therefore, an alternancy of sliding (subdiffusive) with hopping and intersegmental transfer (superdiffusive) mechanisms show important advances for protein-DNA interactions.

## 1. INTRODUCTION

Diffusion—the net movement of particles in an environment, generally from a region of higher concentration to a region of lower concentration—is ubiquitous in natural and man-made systems. In the absence of obstacles to diffusion and traps, the diffusive particles describe a random walk motion on the environment, such that their mean squared displacements (MSD) scale linearly with time,  $\langle x^2 \rangle \propto t$ . This process is known as normal diffusion. However, the existence of obstacles in the environment may trigger long-jumps of the diffusive particle [2–4], such that the mean displacement of the particles is bigger than that of the normally diffusing ones in the same period of time, i.e.,  $\langle x^2 \rangle \propto t^{\alpha > 1}$ . This type of process is known as superdiffusive. On the other hand, it is possible that the environment has regions acting as traps for the particles, where they are retained for longer times than in a normal diffusive process. In this case,  $\langle x^2 \rangle \propto t^{\alpha < 1}$ , and the process is known as subdiffusive. From the modeling perspective there are several approaches to describe anomalous (sub- and super-) diffusion [5, 6]. From a physical perspective these processes have analogues in terms of anomalous heat conduction [7], where normal diffusion implies normal heat conduction, superdiffusion implies anomalous heat conduction with a divergent thermal conductivity and subdiffusion implies anomalous heat conduction with a convergent thermal conductivity. In the last case the system is a thermal insulator in the thermodynamic limit.

It has been remarked that subdiffusion may arise as the result of the coexistence of time-periods dominated by normal transport with periods in which there is no effective transport. The last can emerge when the diffusive particle is temporarily trapped as a result of geometrical complexity and interactions with the environment. This could be clearly the case of the travel of contaminants in groundwater, which display much longer times than the ones expected from the classic diffusion. The motion of proteins while sliding on DNA during target search is believed to be subdiffusive in general [8]. Simulations results for the case of T7 RNA polymerase promoter search on T7 DNA has been found to be subdiffusive for short times and asymptotically approaching normal diffusion [9]. More recent intensive computational simulations also pointed out the important role of subdiffusive process in the diffusive search of proteins for their specific binding sites on DNA in the presence of the macromolecular crowding in cells [10]. Nowadays it is well established that the molecular crowding of the internal cellular environment induces the emergence of anomalous subdiffusion of cytoplasmic macromolecules. This has been verified by means of fluorescence correlation spectroscopy and computer simulations [11], fluorescence correlation spectroscopy [12], and by tracking fluorescently labeled mRNA molecules [13]. The complexities of the process where studied with globular proteins dispersed in aqueous solution of poly(ethylene oxide) (PEO) to mimic a crowded environment. Using state-of-the-art neutron spin echo (NSE) and small-angle neutron scattering (SANS) techniques it was observed a fast dynamic corresponding to diffusion inside a trap built by the polymer mesh with slower process corresponding to the long time diffusion on macroscopic length scales [14]. It has also been found that water molecules jump randomly between trapping sites on protein surfaces, giving rise to subdiffusion. At longer times the subdiffusive exponent gradually increases towards normal diffusion due to a many-body volume-exclusion effect [15].

The intermittency of fast and slow processes as the one described by the globular proteins in a crowded environment [14] can also be found in other scenarios. For instance, it has been reported that a proliferating, diffusing tumor within different surrounding tissue conditions migrates not only by using normal diffusion, but also using combinations of subdiffusion, superdiffusion, and even ballistic diffusion, with increasing mobility of the tumor cell when haptotaxis

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