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Non-Brownian diffusion in lipid membranes: experiments and simulations

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The dynamics of constituents and the surface response of cellular membranes—also in connection to the binding of various particles and macromolecules to the membrane—is still a matter of controversy in the membrane biophysics community, particularly with respect to crowded membranes of living biological cells. We here put into perspective recent single particle tracking experiments in the plasma membranes of living cells and supercomputing studies of lipid bilayer model membranes with and without protein crowding. Special emphasis is put on the observation of anomalous, non-Brownian diffusion of both lipid molecules and proteins embedded in the lipid bilayer. While single component, pure lipid bilayers in simulations exhibit only transient anomalous diffusion of lipid molecules on nanosecond time scales, the persistence of anomalous diffusion becomes significantly longer ranged on the addition of disorder—through the addition of cholesterol or proteins—and on passing of the membrane lipids to the gel phase. Concurrently, experiments demonstrate the anomalous diffusion of membrane embedded proteins up to macroscopic time scales in the minute time range. Particular emphasis will be put on the physical character of the anomalous diffusion, in particular, the occurrence of ageing observed in the experiments—the effective diffusivity of the measured particles is a decreasing function of time. Moreover, we present results for the time dependent local scaling exponent of the mean squared displacement of the monitored particles. Recent results finding deviations from the commonly assumed Gaussian diffusion patterns in protein crowded membranes are reported. The properties of the displacement autocorrelation function of the lipid molecules are discussed in the light of their appropriate physical anomalous diffusion models, both for non-crowded and crowded membranes. In the last part of this review we address the upcoming field of membrane distortion by elongated membrane-binding particles. We discuss how membrane compartmentalisation and the particle-membrane binding energy may impact the dynamics and response of lipid membranes.

I. ANOMALOUS DIFFUSION

On a molecular level the diffusion of reactive particles until their mutual encounter and subsequent reaction is a fundamental mechanism. In fact in 2016 we celebrate the centenary of Marian Smoluchowski's ground breaking mathematical analysis of this problem [1]. Most studies applying this approach to diffusion limited molecular reaction scenarios consider the Brownian motion of the reacting molecules, characterised by a Gaussian spreading of the probability density function $P(\mathbf{r},t)$ of the particle under consideration, in conjunction with the linear time dependence

$$\langle \mathbf{r}^2(t)\rangle \simeq K_1 t \tag{1}$$

of the mean squared displacement with diffusivity K_1, defined in terms of the probability density function $P(\mathbf{r},t)$ to find the particle at position $\mathbf{r}$ at time t through the expectation [2]

$$\langle \mathbf{r}^2(t)\rangle = \int \mathbf{r}^2 P(\mathbf{r},t) d^3\mathbf{r}. \tag{2}$$

For two molecules a and b with cumulative radius $r = r_a + r_b$ and diffusivity $K_1 = K_1^a + K_1^b$ that instantaneously react upon encounter, the Smoluchowski rate becomes $k = 4\pi K_1 r$ in three spatial dimensions [1]. This rate can only be enhanced when additional mechanisms come into play, such as active reactant transport [3, 4] or the dimensional reduction due to intermittent one-dimensional sliding along the DNA of DNA binding proteins in the facilitated diffusion model [5–7].

Yet, in many systems significant deviations from the normal diffusive law (1) are routinely observed [8–10]. Methods such as fluorescence correlation spectroscopy (FCS), fluorescent recovery after photobleaching (FRAP), and single particle tracking often reveal power-law forms

$$\left\langle \mathbf{r}^2(t)\right\rangle \simeq K_\beta t^\beta \tag{3}$$

for the mean squared displacement with the generalised diffusion coefficient K_β of physical dimension $\mathrm{cm}^2/\mathrm{sec}^\beta$. Depending on the value of the anomalous diffusion exponent β one distinguishes between subdiffusion ($0 < \beta < 1$) and superdiffusion ($\beta > 1$) [9–14].

Such anomalous diffusion may correspond to a range of different physical processes. All of these different processes exhibit the same power-law scaling of the mean squared displacement (3), however, their other dynamic properties may differ significantly [12–14]. These properties in turn critically affect the way we need to extract parameters from measurements, and the predictions of our quantitative models for followup processes such as

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