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Comment

Dynamic fluctuations in single-molecule biophysics experiments Comment on "Extracting physics of life at the molecular level: A review of single-molecule data analyses" by W. Colomb and S.K. Sarkar

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Single-molecule biophysics includes the study of isolated molecules and that of individual molecules within living cells. In both cases, dynamic fluctuations at the nanoscale play a critical role. Colomb and Sarkar emphasize how different noise sources affect the analysis of single molecule data [1]. Fluctuations in biomolecular systems arise from two very different mechanisms. On one hand thermal fluctuations are a predominant feature in the behavior of individual molecules. On the other hand, non-Gaussian fluctuations can arise from inter- and intramolecular interactions [2], spatial heterogeneities [3], non-Poisson external perturbations [4] and complex non-linear dynamics in general [5,6].

Thermal fluctuations are intrinsically Gaussian and the fluctuation-dissipation theorem provides a connection between the response of the system to a small external perturbation and the internal fluctuations in the absence of the disturbance [7]. For example, a DNA hairpin is observed to alternate between folded and unfolded states [1,8] and single ion channels exhibit fluctuations between open and closed states [9]. Further, thermal fluctuations are needed for many biological functions such as the transduction of chemical energy into motion by molecular motors, the translocation of biopolymers through membrane pores, and cell migration induced by actin polymerization [10].

Fluctuations due to interactions with a complex biological environment can lead to non-Gaussian fluctuations with many interesting physical phenomena. For example, interactions within the cell may be non-Markovian with binding times distributed according to power laws. This type of statistics was observed in the motion of ion channels on the plasma membrane of mammalian cells [11,12] and in the motion of lipid and insulin granules in the cytoplasm [13,14]. These systems are not ergodic and therefore the time averages vary from one particle to the next, even though all particles may be identical and they may explore the same substrate [2]. Then, the parameters estimated from individual trajectories, such as the mean squared displacement, exhibit a very large scatter.

One of the main factors where single molecule experiments shed useful information lies in the fact that the whole distribution is available in the measurements and not only the mean of the observed parameter. As a consequence

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we can study the interactions in a cell by not only measuring average values, as in ensemble measurements, but by accessing the full information within the probability density functions. These data lead to new information with important physiological implications. First, many biological systems are governed by rare events. For example, the internalization of cargo by clathrin-mediated endocytosis requires clathrin coats to mature over times longer than one minute. However, most clathrin coats end up in abortive short events [15]. Second, when one studies characteristic times by ensemble measurements, it is typically assumed that the distributions are well-behaved in the sense that the first and second moments are finite. However, power law distributions can have infinite moments and the central limit theorem breaks down. Furthermore, when the stochastic process under investigation does not have a finite first moment, the only characteristic time of the experiment is the measurement time [6]. Thus, the estimated parameters do not converge in the long experimental time. This issues present challenges in the analysis of non-Markovian systems.

Single-molecule measurements are strongly affected by noise. Nevertheless, in many instances the fluctuations in the system provide the ground for the study of physical phenomena and for the understanding of biological function. It is foreseen that single-molecule biophysics in combination with stochastic analyses will continue to yield scientific breakthroughs in many fascinating areas. This kind of experimental research was only enabled in the last few years with the advent of important technological advances that made possible high-accuracy and high-throughput measurements at the single-molecule level.

References

[1] Colomb W, Sarkar SK. Extracting physics of life at the molecular level: a review of single-molecule data analyses. Phys Life Rev 2015;13:107–37 [in this issue].
[2] Barkai E, Garini Y, Metzler R. Strange kinetics of single molecules in living cells. Phys Today 2012;65(8):29–35.
[3] Cherstvy AG, Metzler R. Nonergodicity, fluctuations, and criticality in heterogeneous diffusion processes. Phys Rev E 2014;90(1):012134.
[4] Allegrini P, et al. Fluctuation-dissipation theorem for event-dominated processes. Phys Rev Lett 2007;99(1):010603.
[5] Wang B, et al. When Brownian diffusion is not Gaussian. Nat Mater 2012;11(6):481–5.
[6] Metzler R, et al. Anomalous diffusion models and their properties: non-stationarity, non-ergodicity, and ageing at the centenary of single particle tracking. Phys Chem Chem Phys 2014;16(44):24128–64.
[7] Kubo R. The fluctuation–dissipation theorem. Rep Prog Phys 1966;29(1):255.
[8] Woodside MT, et al. Nanomechanical measurements of the sequence-dependent folding landscapes of single nucleic acid hairpins. Proc Natl Acad Sci USA 2006;103(16):6190–5.
[9] Hille B. Ion channels of excitable membranes. 3rd edition. Sunderland, MA: Sinauer Associates; 2001.
[10] Peskin CS, Odell GM, Oster GF. Cellular motions and thermal fluctuations: the Brownian ratchet. Biophys J 1993;65(1):316.
[11] Weigel AV, et al. Ergodic and nonergodic processes coexist in the plasma membrane as observed by single-molecule tracking. Proc Natl Acad Sci USA 2011;108(16):6438–43.
[12] Weigel AV, Tamkun MM, Krapf D. Quantifying the dynamic interactions between a clathrin-coated pit and cargo molecules. Proc Natl Acad Sci USA 2013;110(48):E4591–600.
[13] Jeon JH, et al. In vivo anomalous diffusion and weak ergodicity breaking of lipid granules. Phys Rev Lett 2011;106(4):048103.
[14] Tabei SMA, et al. Intracellular transport of insulin granules is a subordinated random walk. Proc Natl Acad Sci USA 2013;110(13):4911–6.
[15] Loerke D, et al. Cargo and dynamin regulate clathrin-coated pit maturation. PLoS Biol 2009;7(3):628–39.