Cumulative Area Tracking: A New Single-Molecule Tracking Method for Simultaneous Characterization of Diffusion and Conformational Dynamics

Maged F. Serag, Maram Abadi, Satoshi Habuchi
Biological and Environmental Sciences and Engineering Division, King Abdullah University of Science and Technology (KAUST)
P.O. Box 4700 KAUST, Thuwal 23955-6900, Saudi Arabia
E-mail: satoshi.habuchi@kaust.edu.sa

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Providing unprecedented insights into diffusional dynamics of heterogeneous systems in material and life sciences, single molecule localization and tracking (SMLT) has been regarded as a powerful tool for analyzing dynamics of individual molecules not masked by ensemble averaging. Although, the long-established SMLT technology provides accurate spatiotemporal locations of single molecules, the method cannot provide essential information about structural and conformational dynamics of the molecules. Furthermore, statistical and localization errors result in broader distribution of diffusion coefficients.

Here we present a new single molecule imaging technique, cumulative area (CA) tracking, which provides an efficient solution to the challenges described above. Our new method expresses molecular motion in terms of the time-dependent increase of the cumulative area occupied by the molecule in space. By analyzing fluorescent nanospheres and dsDNA molecules of different lengths and topological forms, we demonstrate that CA tracking surpasses the conventional single-molecule localization method in terms of accuracy of determined diffusion coefficients. We also demonstrate that CA tracking can distinguish diffusion modes and provides conformational relaxation time of the structurally flexible dsDNA molecules along with the diffusion coefficients [1].

Using CA tracking, we further investigate the diffusive dynamics and conformational relaxation of entangled polymers, which have been an important but poorly understood question. CA tracking is shown to be remarkably effective for the quantitative characterization of the mode of the diffusive motion of long semiflexible polymers under entangled conditions [2]. Our results point to the critical role of the mutual relaxation of the entangled chains in the motion of a cyclic polymer.