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Inference of protein diffusion probed via fluorescence correlation spectroscopy

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Fluctuations are an inherent part of single molecule or few particle biophysical data sets. Traditionally, "noise" fluctuations have been viewed as a nuisance, to be eliminated or minimized. Here we look on how statistical inference methods – that take explicit advantage of fluctuations – have allowed us to draw an unexpected picture of single molecule diffusional dynamics. Our focus is on the diffusion of proteins probed using fluorescence correlation spectroscopy (FCS). First, we discuss how – in collaboration with the Bustamante and Marqusee labs at UC Berkeley – we determined using FCS data that individual enzymes are perturbed by self-generated catalytic heat (Riedel et al, Nature, 2014). Using the tools of inference, we found how distributions of enzyme diffusion coefficients shift in the presence of substrate revealing that enzymes performing highly exothermic reactions dissipate heat by transiently accelerating their center of mass following a catalytic reaction. Next, when molecules diffuse in the cell nucleus they often appear to diffuse anomalously. We analyze FCS data – in collaboration with Rich Day at the IU Med School – to propose a simple model for transcription factor binding-unbinding in the nucleus to show that it may give rise to apparent anomalous diffusion. Here inference methods extract entire binding affinity distributions for the diffusing transcription factors, allowing us to precisely characterize their interactions with different components of the nuclear environment. From this analysis, we draw key mechanistic insight that goes beyond what is possible by simply fitting data to "anomalous diffusion" models.