Supporting Information for "Rapid and Quantitative Sizing of Nanoparticles Using Three-Dimensional Single-Particle Tracking"

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Sample: Colloidal gold nanoparticles (BBInternational Ltd, UK) were used as received. The samples used in this study had product codes (batch number in parenthesis) of EM.GC80 (6657), EM.GC100 (8319), EM.GC150 (8040), EM.GC200 (8289), and EM.GC250 (7953), and represented particles with nominal diameters 80 nm, 100 nm, 150 nm, 200 nm, and 250 nm, respectively. In an experiment, the sample was diluted in water to a concentration of ~ 2–4×10^8 particles/mL. A 5-μL aliquot was sealed between two glass cover slips (Fisher, 18×18 mm and 24×40 mm) with transparent nail polish, forming a ~ 15-μm thick reservoir.

Data analysis: To suppress photon-counting noise, a very simple form of an auto-regressive (AR) filter was applied to photon counts collected at 100 kHz before they were fed into the proportional-integral-derivative (PID) feedback control loop. The same PID parameters were used for all the experiments reported here. The AR filter allows an efficient estimation of the unknown state recursively from noisy data. In the present implementation, the filtering is accomplished by the following equation, $\tilde{I}_k = \lambda I_k + (1-\lambda)\tilde{I}_{k-1}$, where $\tilde{I}$ is the filtered signal, I is the raw signal, and λ (= 0.003 in the present application) is the AR filter parameter. The subscript *k* denotes the photon-counting sampling index (10 μs per sample), which is different from the position measurement index *i* (100 μs per sample). This digital filter was devised for its analytical tractability and computational efficiency in real-time tracking. Because of the filtering, the apparent diffusion coefficient as computed from the maximum likelihood estimator, $\hat{D}_{app} = \sum_{i=1}^{N} \Delta_i^2 / \left(2N\delta\right)$,[12] is an underestimate by a factor of

$A = [2 - 2(1-\lambda)^{1+m} - 2\lambda - 2m\lambda + m\lambda^2]/[m(-2+\lambda)\lambda]$, where m is the number of photon counting samples within time lag δ, *e.g.*, $m = 50$ with $\delta = 0.5$ ms. A approaches unity at a very large m (long time lag) as expected.

To extract the diffusion coefficient from a 3D-SPT trajectory, the apparent diffusion coefficient $\hat{D}_{app} = \sum_{i=1}^{N} \Delta_i^2 / (2N\delta)$ was first rescaled by A for each axis. At this point, the apparent diffusion coefficient contained contributions from measurement uncertainty, σ_c^2, which was estimated by a least-squares fit to the equation, $\hat{D}_c = \hat{D}_{app} / A - \sigma_c^2 / \delta$, as a function of δ. The first four data points ($\delta \leq 0.4$ ms for data recorded every 100 μs) were excluded from the fitting due to the limited bandwidth (3 kHz) of the capacitive sensor. The measurement uncertainty for a moving particle thus estimated was ~16 nm. Finally, the diffusion coefficient was obtained using $\hat{D}_c = D_{app} / A - \sigma_c^2 / \delta$, evaluated at $\delta = 0.5$ ms. The average value of the three axes is reported.

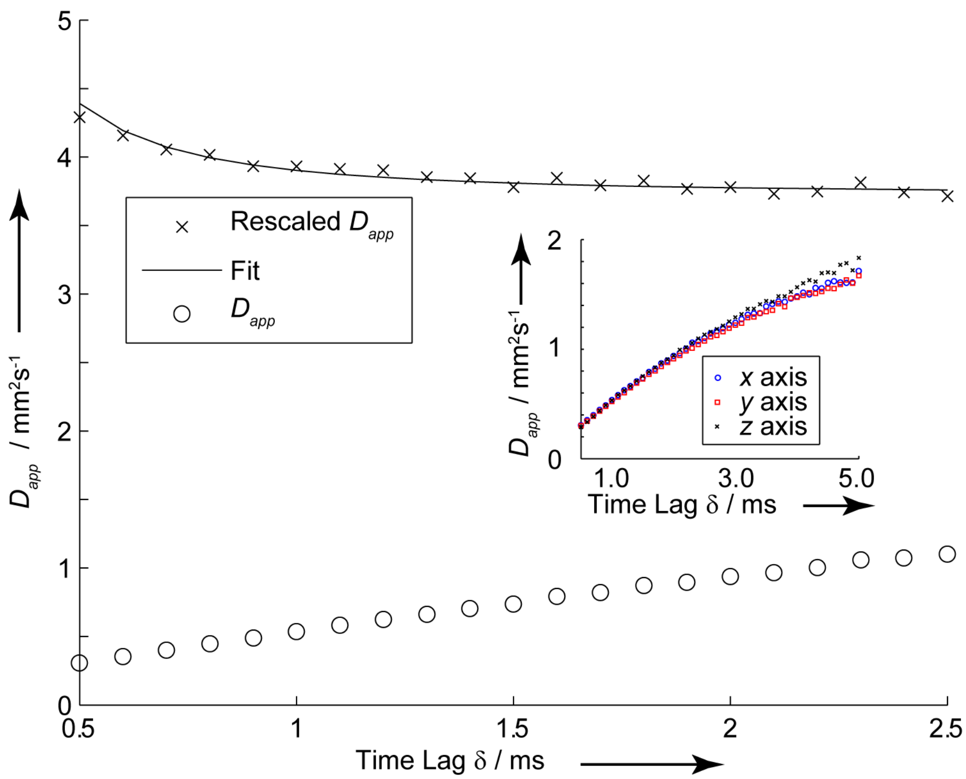

Figure 1. Representative apparent diffusion coefficients D_{app} as a function of time lag δ, prior to (o) and post rescaling (x) by the correction factor A from auto-regressive filter. The inset shows the

consistency among the apparent diffusion coefficients extracted from x, y, and z axes.