where $\hat{\mu}$ is the sample mean for o, the samples in state ~~j~~ m,

$$\hat{\mu} \equiv \frac{1}{N} \sum_{n=1}^{N} o_n \tag{48}$$

This allows us to update μ according to

$$\mu' \sim \mathcal{N}(\hat{\mu}, \sigma^2/N) \tag{49}$$

The conditional distribution of the variance σ^2 is given by

$$\begin{aligned} p(\sigma^2|\mu, \mathbf{o}) &= \frac{p(\mu, \sigma^2|\mathbf{o})}{\int d\sigma^2 \, p(\mu, \sigma^2|\mathbf{o})} \\ &\propto \sigma^{-(N+1)} \exp\left[-\frac{1}{2\sigma^2} \sum_{n=1}^{N} (o_n - \mu)^2 \right] \\ &\propto \sigma^{-(N+1)} \exp\left[-\frac{N\hat{\sigma}^2}{2\sigma^2} \right] \end{aligned} \tag{50}$$

where the quantity $\hat{\sigma}^2$, which is *not* in general identical to the sample variance, is given by

$$\hat{\sigma}^2 \equiv \frac{1}{N} \sum_{n=1}^{N} (o_n - \mu)^2 \tag{51}$$

A convenient way to update $\sigma^2|\mu, \mathbf{o}$ is to sample a random variate y from the chi-square distribution with $N - 1$ degrees of freedom,

$$y \sim \chi^2(N - 1) \tag{52}$$

and then compute the new σ^2 as

$$\sigma^{2\prime} = \frac{N\hat{\sigma}^2}{y} \tag{53}$$

Note that μ and σ^2 can be updated in either order, but the *updated* values of μ or σ^2 must be used in sampling the updated σ^2 or μ, and vice-versa.

IV. APPLICATION TO FORCE SPECTROSCOPY

We illustrate the BHMM approach in characterizing the average forces and transition rates among metastable states of the p5ab RNA hairpin in a single optical trap.

[JDC: I have the data for this — I just have to rerun it and generate plots, as well as come up with something coherent to say here.]

The p5ab RNA hairpin from *Tetrahymena thermophilia* was provided by Jin-Der Wen, and prepared as previously described [29]. Within the population RNA hairpin molecules in the examined sample, the behavior fell into one of two types, exhibiting either apparent two-state (as reported previously [29]) or three-state behavior (studied here). For the purposes of testing this method, we used only data that exhibited three states upon inspection. [JDC: Give some plausible explanations for why there might be some small population with three apparent states.]

The instrument used in this experiment was a dual-beam counterpropagating optical trap with a spring constant of 0.1 pN/nm. A piezoactuator controlled the position of the trap and allowed position resolution to within 0.5 nm [30]. Drift in the instrument was less than 1 nm/minute resulting in a constant average force within 0.1 pN over the course of typical experiment. For the constant trap position experiments, higher frequency data was recorded at 50 kHz recording the voltage corresponding to the force on the tether directly from the position-sensitive detectors.

V. DISCUSSION

- Advantages over other approaches
- Extensions to multiple observables
- Extensions to nonequilibrium measurements, such as Norbert Scherer data?
- Extension to sampling over multiple states

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