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COMMENT

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Reply to the 'Comment on "A symmetrical method to obtain shear moduli from microrheology"' by M. Tassieri, *Soft Matter*, 2018, 14, DOI: 10.1039/C8SM00806J

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The Comment on our paper introducing "a symmetric method to obtain shear moduli from microrheology" proposes an interpolation method to generate oversampled data from an original time series that are then used to approximate shear moduli at frequencies "beyond the Nyquist frequency." The author states that this can be done without the use of "preconceived fitting functions," implying that the results are unique and reliable. We disagree with these assertions. While it is possible to generate reasonable looking transforms at frequencies above the Nyquist limit by interpolation, any results obtained above the Nyquist limit will be questionable at best. Moreover, while the cubic spline interpolation the author uses may be standard, it constitutes a particular "preconceived" fit and produces oversampled data that are not unique.

The point of our recent paper[1] was to develop and test a direct analysis method to extract the frequency-dependent response of a soft material from the displacement fluctuations of embedded probes, using the fluctuation–dissipation theorem. The application we had in mind was to time-series such as those obtained in microrheology experiments, such as those in ref. 1 and cited therein. We assumed that the data represent a continuous time-dependent process that is sampled at a fixed rate $f_s = 1/\Delta t$, where Δt is the sampling interval. For such a sampling method, the Nyquist–Shannon theorem specifies the frequency $f_s/2$ as the upper bound of frequencies at which the corresponding frequency-dependent transform can still be reliably determined. We applied our method to both real and synthetic sampled data to test its reliability within the range of frequencies limited by the Nyquist–Shannon theorem.

In the Comment,[2] the author proposes an extension of our method in ref. 1 to determine the complex shear modulus "beyond the Nyquist frequency." For this, the author uses spline fitting and interpolation of the mean-squared displacement (MSD) to generate an oversampled data set, which is then analyzed. As with any time series, it is always possible to artificially generate an oversampled MSD with a higher sampling rate using some interpolation method. This typically results in transformed quantities that appear well-behaved beyond the fundamental Nyquist–Shannon limit. It is important to note, however, that interpolation and oversampling such as proposed in the Comment is not unique, meaning that different results for the frequency regime above the Nyquist–Shannon limit can all be consistent with the same original sampled data. Fundamentally, one can therefore not be sure that results obtained above the Nyquist frequency are meaningful or reliable. In other words, as the Comment author himself noted in the earlier ref. 3, "no real information exists above the Nyquist frequency." For this reason, we did not employ such oversampling.

We further argue that it is dangerous to rely on such oversampling specifically in the context of microrheology, which is frequently used to identify high-frequency relaxation mechanisms in soft matter systems. Rapid physical relaxation mechanisms may be absent from time series recorded at low frequencies. A good example of high frequency effects is decreased compliance due to inertia, which causes significant deviations from simple power law behavior in the high-frequency response of viscoelastic media.[4] Importantly, this effect is fully describable by the linear response formalism we reviewed in Sections 2.1–2.3 in ref. 1, *e.g.*, in the unsteady Stokes regime of a liquid, even if the

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Stokes relation or its generalization (*e.g.*, eqn (3) and (4) in the Comment) are violated. Here, interpolation of the kind proposed in the Comment would likely fail to capture inertial effects that might lie just beyond the Nyquist frequency, although it might still be useful in suppressing aliasing effects.

Thus, while we agree with the Comment author that oversampling can yield results over a frequency range that exceeds the Nyquist frequency, we disagree that oversampling delivers reliable results beyond this fundamental limit. Moreover, we disagree with the author that his technique ''does not need preconceived fitting functions.'' Beginning with an original data set obtained at a finite sampling rate, there is no unique or universal interpolation that can be used to unambiguously generate an extended, or oversampled data set. Interpolation necessarily makes use of a ''preconceived'' function, such as the cubic spline used in the Comment. While such a spline fit may be standard, it is not unique.

In addition to the proposed interpolation, the Comment compares the results of our approach in ref. 1 with a similar transformation method from ref. 3, as applied to the oversampled data. Apart from some small differences at the highest frequencies, the author concludes that both methods yield good approximations over the range compared. For the reasons stated above, this comparison should only be made up to the Nyquist frequency. As shown in the Comment, interpolation can be useful for removing the most obvious artifacts arising from aliasing, such as the strong downturn in K' apparent Fig. 1 of the Comment (reproduced from ref. 1). But, as shown in ref. 1, this downturn was only apparent in approximately the final factor of two in frequency near the Nyquist limit, beyond which no reliable information can be extracted. Thus, the advantage of interpolation is limited and primarily cosmetic in our view.

Concerning the accuracy of the two approaches shown in Fig. 2 of the Comment, we agree that the approach in ref. 3 appears to offer a wider range of data accurate to 1%. We note, however, that this method exhibits larger relative errors (approaching 10% in G'') than our approach does at the Nyquist frequency. Moreover, the Comment shows that the relative error of the approach in ref. 3 systematically increases more rapidly with frequency than the transform we employed in ref. 1. Thus, while any comparison is likely to depend on the system studied, it is unclear whether the method proposed in the Comment delivers higher overall accuracy.

In the penultimate paragraph, the Comment mentions a ''discrepancy between the two outputs'' and suggests ''possible coding/indexing issues'' in the method we used. We are not sure what discrepancy the author is referring to here, since this note was preceded by a comparison of our original figure (reproduced in the Comment as Fig. 1) and the analysis of interpolated data. Obviously, a difference is expected between interpolated and non-interpolated data. If the discrepancy refers to the difference we observed between our method and the method of ref. 3, as applied to non-interpolated data, such a difference is also to be expected since the algorithms are different. We note that the Comment also reports a difference between these methods in Fig. 2. By writing ''when the analytical method introduced by Nishi *et al.* is accurately implemented...'', the author of the Comment suggests that the algorithm in the Appendix of the Comment corrects an error in our analysis. In order to exclude that possibility, we have confirmed that our code and that of the Appendix yield identical results for the MSD data we used in our original Fig. 2 (Fig. 1 in the Comment). We agree with the Comment that the initial point of the MSD equals zero, and we use this fact.

Beyond our main concern over the reliability of the interpolation proposed in the Comment, it is interesting to note that the actual transformations used in eqn (13) and (14) of ref. 1 and eqn (5) of the Comment differ in the order of the time derivative of the MSD used. In ref. 1, we use a single time derivative, while eqn (5) of the Comment is based on the second derivative of the MSD. We argue that the former is simpler and more direct, although we note that there can be an advantage of the second-derivative approach of ref. 3 for systems that are fluid-like at long times. In this case the second derivative vanishes at long times, while the first derivative does not. But since the main goal of both ref. 1 and 3 is to obtain more accurate high-frequency moduli, the long-time or low-frequency limit is of less importance. Moreover, in a typical optical trapping-based microrheology experiment, the probe particles tend to be physically confined, so that the long-time dynamics of a fluctuating probe would be regularized, even in a fluid.

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Conflicts of interest

There are no conflicts to declare.

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