Costa, Goldberger, and Peng Reply: The authors of the Comment [1] raise a point that was not discussed in our paper [2] due to page limitations. The multiscale entropy (MSE) [2] method is aimed at evaluating the complexity of time series. It is based on the analysis of the entropy values assigned not only to the original time series but also to coarse-grained time series, each of which represents the system's dynamics on a different scale.

The entropy assigned to a time series takes into account both its standard deviation (SD) and its correlation properties. However, there is no universal relationship between entropy and SD. Signals with higher variance may or may not have higher entropy, depending on the correlation properties. We illustrate both cases: (1) Consider stochastic variables that are completely independent (without correlations). The variables with larger variances will have higher entropy. (2) Consider a periodic signal with variance $|x|$ and a random signal with variance $|y|$. The entropy for the random signal is higher than the entropy for the periodic signal, even if $|x| \gg |y|$.

For a very simple time series, belonging to one of the two groups comprising completely ordered or completely disordered signals, it is possible to evaluate, separately, the contributions of the SD and the correlation properties to the entropy value. However, this is not the case for complex signals, which may incorporate both random and deterministic components, as Nikulin *et al.* imply in their Comment. In general, the degree of irregularity of a complex signal is a property measured by entropy that cannot be entirely captured by the SD or correlation measures, individually or in combination.

In our Letter, we used sample entropy (SampEn) to evaluate the degree of randomness of a single time series. This algorithm requires that we specify the values of two parameters: m and r, where m defines the length of the patterns that are compared to each other, and r the similarity criterion. Two patterns of length m, $u[i]$ and $u[j]$, are similar if the distance between them is $\leq r$. r is defined as a percentage of the SD, and not as an absolute value. This particular implementation is commonly used in heart rate variability analysis because it is well established that SD alone can be a useful indicator of health status. Use of the parameter r, a percentage of SD, therefore probes information that is independent of the time series SD.

We considered $r = 0.15 \times \mathrm{SD}$ for all groups, which corresponds to normalizing all time series by their SD. Next, we coarse grained the time series and calculated their entropy. We did not renormalize the coarse-grained time series because, after the initial normalization, subsequent changes in SD of coarse-grained time series contain information about the temporal structure of the original time series that should be accounted for by an entropy measure.

Using this approach, we consistently observed that $1/f$ noise is more complex than white noise. As applied to the heart rate time series (Fig. 1), our method shows that healthy dynamics are more complex than pathologic dynamics, which is in accord with the unifying concept that biologic complexity degrades with disease and aging. In Fig. 1, top plot, we present the MSE results for heart rate time series derived from healthy subjects and congestive heart failure patients [2]. The bottom plot shows the ratios between the mean values of SD for the coarse-grained series and the mean values of SD for the original time series. As anticipated, the small variations in SD do not account for the prominent differences in entropy.

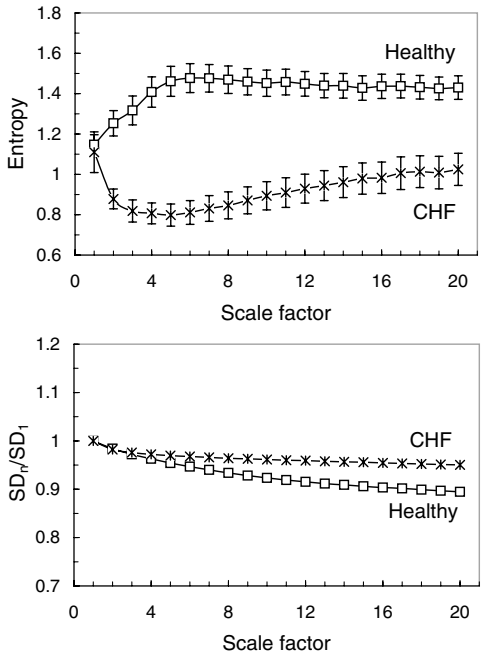

FIG. 1. Top: MSE analysis of the cardiac interbeat interval time series from healthy subjects and subjects with congestive heart failure (CHF). Error bars indicate standard error. Adapted from Ref. [2]. Bottom: Ratio between the mean values of standard deviations for the coarse-grained time series (SD_n) and the mean values of standard deviations for the original time series (SD_1), plotted against scale factor.

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