

**Costa, Goldberger, and Peng Reply:** Wessel *et al.* [1] comment on our recent Letter [2] regarding multiscale entropy (MSE) analysis of time series. Unfortunately, they misrepresented the main purpose of our report.

The central point of our Letter was to introduce a new method of measuring complexity compatible with the unifying concept that healthy systems, regulated by a myriad of control mechanisms operating on multiple time scales, are more complex than pathologic and aging systems in which such mechanisms become degraded.

Furthermore, our method applies both to physiologic and physical time series. In particular, we addressed a long-standing problem concerning the relative complexity of correlated and uncorrelated signals. We showed that long-range correlated ( $1/f$ ) noise is more complex than uncorrelated (white) noise.

Next, we demonstrated that the MSE approach, when applied to heart rate time series, yields physiologically consistent results: the fluctuations of healthy systems show higher complexity than those of aging and pathologic systems. Prior studies using traditional (single-scale) entropy measurements yielded contradictory results, indicating higher complexity for certain pathologic processes with irregular outputs, such as atrial fibrillation (AF). Most heart rate variability techniques, including the method of Wessel *et al.* (POLVAR20) [3], avoid this inconsistency by excluding AF data. Our method, in contrast, shows that increased irregularity is not necessarily indicative of increased complexity. Therefore, contrary to the statement of Wessel *et al.*, the inclusion of AF data is of crucial importance in evaluating the complexity of cardiac physiologic time series. In contrast, POLVAR20 does not provide an index of signal complexity. This statistic is applicable only to certain classes of heartbeat interval time series and, therefore, not relevant to the general problem we address.

Wessel *et al.* suggest that our finding of increased complexity for healthy subjects versus those with congestive heart failure (CHF) is purely due to age differences (i.e., the healthy group was younger). To address this contention, we analyze additional datasets available online [4] which are biased against our initial results. We compare the heart rate dynamics of 22 healthy elderly subjects, aged  $69 \pm 3$  yr with that of 14 younger CHF subjects, aged  $56 \pm 12$  yr. We find that the healthy older subjects still show significantly higher complexity than the younger group with heart failure (Fig. 1), contradicting the assertion of Wessel *et al.*

The point of our Letter, however, was not to make any claims about the relative merits of the MSE method compared with the techniques for heart rate variability analysis. But we note that the utility of the MSE method has been subsequently validated on independent data, also available online [4,5], as part of the Computers in Cardiology Challenge 2002, which was devoted to discriminating between synthetic and physiologic time

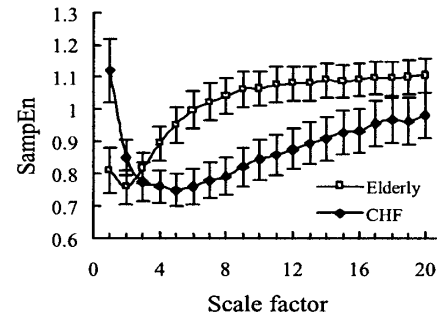


FIG. 1. MSE analysis of the interbeat interval time series derived from elderly healthy subjects and younger subjects with congestive heart failure. Symbols represent mean entropy values (SampEn [1]) and bars represent standard error. The differences between SampEn values for elderly and CHF subjects are significant ( $p < 0.05$ , Mann-Whitney test) from scale 5 to scale 13, indicating that the findings are not simply attributable to an age effect. The values of the parameters used to calculate SampEn are  $m = 2$ ,  $r = 0.15$ , and  $N = 30\,000$  [1].

series. The MSE method revealed that the heartbeat interval time series of healthy subjects are more complex than synthetic time series. The MSE method was able to identify 20 out of 22 synthetic time series (90% accuracy).

Finally, we note that the MSE method is applicable to other types of time series. For example, we recently applied the MSE method to human gait data and showed that time series derived from healthy subjects under spontaneous walking conditions are more complex than those obtained under slow, fast, or metronomically paced protocols [6]. These results are also consistent with the concept that healthy physiologic systems are the most complex.

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