# Generalized Multiscale Entropy (GMSE) Analysis: Quantifying the Structure of Time Series' Volatility

Madalena D. Costa and Ary L. Goldberger
Beth Israel Deaconess Medical Center, Boston, USA

A detailed description of the generalized multiscale entropy algorithm (GMSE) and its application can be found in:

- Costa M., Goldberger A.L. Generalized Multiscale Entropy Analysis: Application to Quantifying the Complex Volatility of Human Heartbeat Time Series. *Entropy* 2015;**17**:1197-1203.

Please cite this publication when referencing this material, and also include the standard citation for PhysioNet:

- Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PCh, Mark RG, Mietus JE, Moody GB, Peng C-K, Stanley HE. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation* **101**(23):e215-e220

The software described in this tutorial is available here.

# 1 Background

The original multiscale entropy (MSE) method [1, 2] quantifies the complexity of the temporal changes in one specific feature of a time series: the local mean values of the fluctuations. The method comprises two steps: 1) coarse-graining of the original time series, and 2) quantification of the degree of irregularity of the coarse-grained (C-G) time series using an entropy measure such as sample entropy (SampEn) [3].

The generalized multiscale entropy (GMSE) method [4] quantifies the complexity of the dynamics of a set of features of the time series related to local sample moments. The method differs from the original MSE in the way that the C-G time series are computed. In the original method, the mean value is used to derive a set of representations of the original signal at different levels of resolution. This choice implies that information encoded in features related to higher moments is discarded. The coarse-graining procedure in the generalized algorithm extracts statistical features such as the variance (standard deviation [SD] or mean absolute deviation [MAD]), skewness, kurtosis, etc, over a range of time scales. This tutorial focuses primarily on the quantification of the information encoded in fluctuations in standard deviation.

We use a subscript after MSE to designate the type of coarse-graining employed. Specifically, $\text{MSE}_\mu$, $\text{MSE}_\sigma$ and $\text{MSE}_{\sigma^2}$ refer to MSE computed for mean, SD and variance C-G time series, respectively.

**CONCEPTUAL FRAMEWORK OF MULTISCALE ENTROPY ALGORITHMS**

For a dynamical property of interest, such as mean or standard deviation, MSE algorithms comprise two sequential procedures:

1. Extracting representations of the systems dynamics at different levels of resolution, i.e., deriving the coarse-grained time series and
2. Assessing the degree of unpredictability of the C-G time series using an entropy measure, e.g., sample entropy.

As noted above, in the original MSE method ($\text{MSE}_\mu$) the property of interest is the local mean value. The C-G time series capture fluctuations in local mean value for pre-selected time scales. In the original application, such C-G time series were obtained by dividing the original time series into non-overlapping segments of equal length and calculating the mean value of each of them. However, other approaches for extracting the same "type" of information (local mean) can also be considered, including low pass filtering the original time series using Fourier analysis, among others (e.g., the empirical mode decomposition) methods.

The GMSE method expands the original MSE framework to other properties of a signal. Here, we address the quantification of information encoded in the fluctuations of the "volatility" of the signal.

Figure 1 shows the interbeat interval (RR) time series from a healthy subject, simulated 1/f noise and their SD C-G time series for scales 5 and 20. The fluctuation patterns of the physiologic C-G time series appear more unpredictable, "less uniform" and more "bursty," than those of simulated 1/f noise.

Figure 2 shows $\text{MSE}_\sigma$ (top panels) and $\text{MSE}_{\sigma^2}$ (bottom panels) analyses of physiologic and simulated long-range correlated (1/f) noise time series. The physiologic time series are the RR intervals (left panels) from healthy young to middle-aged ($\leq 50$ years) and healthy older ($> 50$ years) subjects and patients with chronic (congestive) heart failure (CHF). The time series are available on PhysioNet: i) 26 healthy young

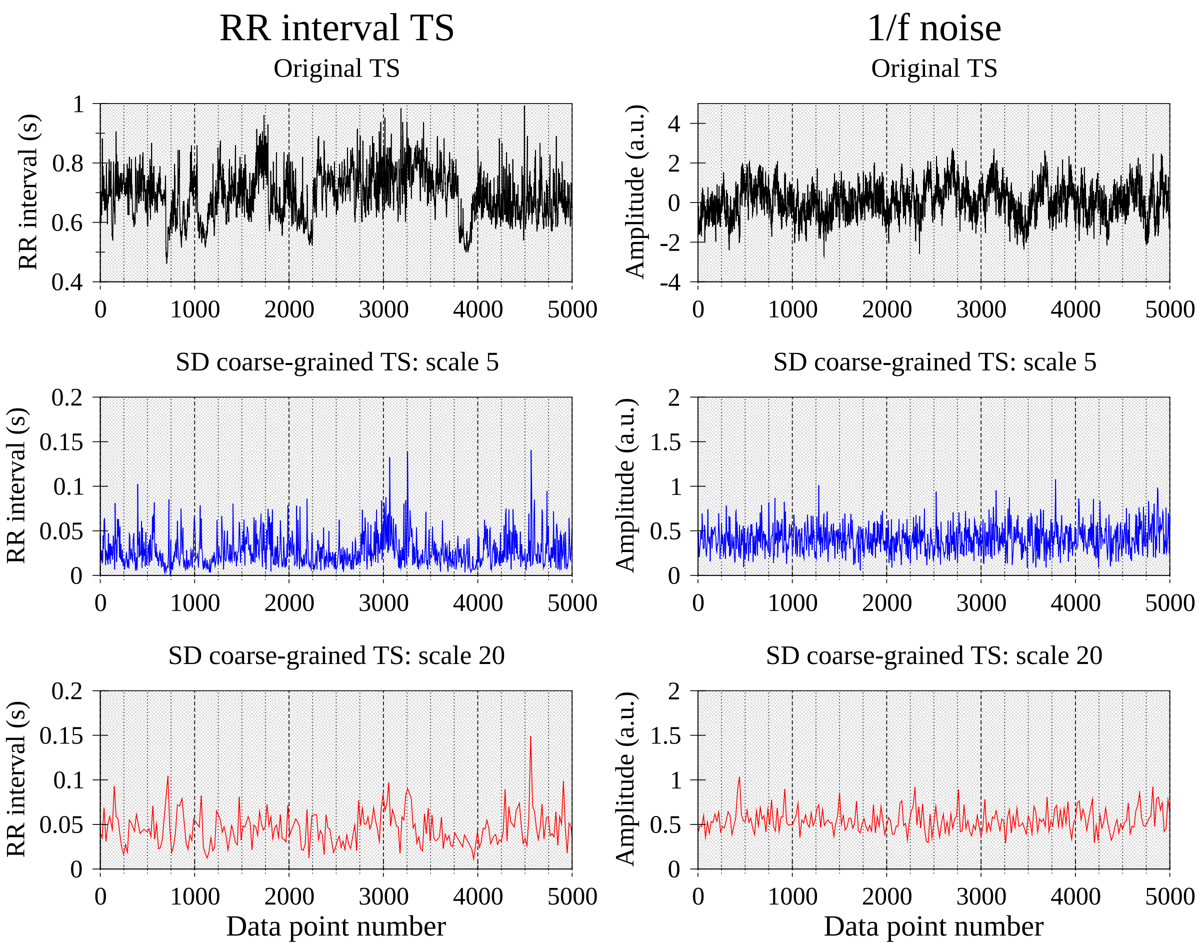


Figure 1: Original (top panels) and standard deviation (SD) coarse-grained time series (TS), obtained using a moving window comprising five (middle panels) and 20 (bottom panels) data points, of the cardiac interbeat (RR) interval from a healthy subject (left panels) and a simulation of long-range correlated (1/f) noise (right panels).

subjects and 46 healthy older subjects (nsrdb, nsr2db) ii) 32 patients with CHF class III and IV (chfdb, chf2db).

Entropy over the pre-selected range of scales was higher for 1/f than white noise, both for SD and variance C-G time series. With respect to the RR interval time series, entropy values were on average higher for the group of healthy young subjects than for the group of healthy older subjects. In addition, the entropy values for the group of CHF patients were, on average, the lowest. The results were qualitatively the same for SD and variance C-G time series.

These findings are consistent with those derived from traditional (mean C-G) MSE analyses. They indicate that: 1) 1/f noise processes are more complex than uncorrelated random ones; 2) the complexity of heart rate dynamics degrades with aging and heart disease.

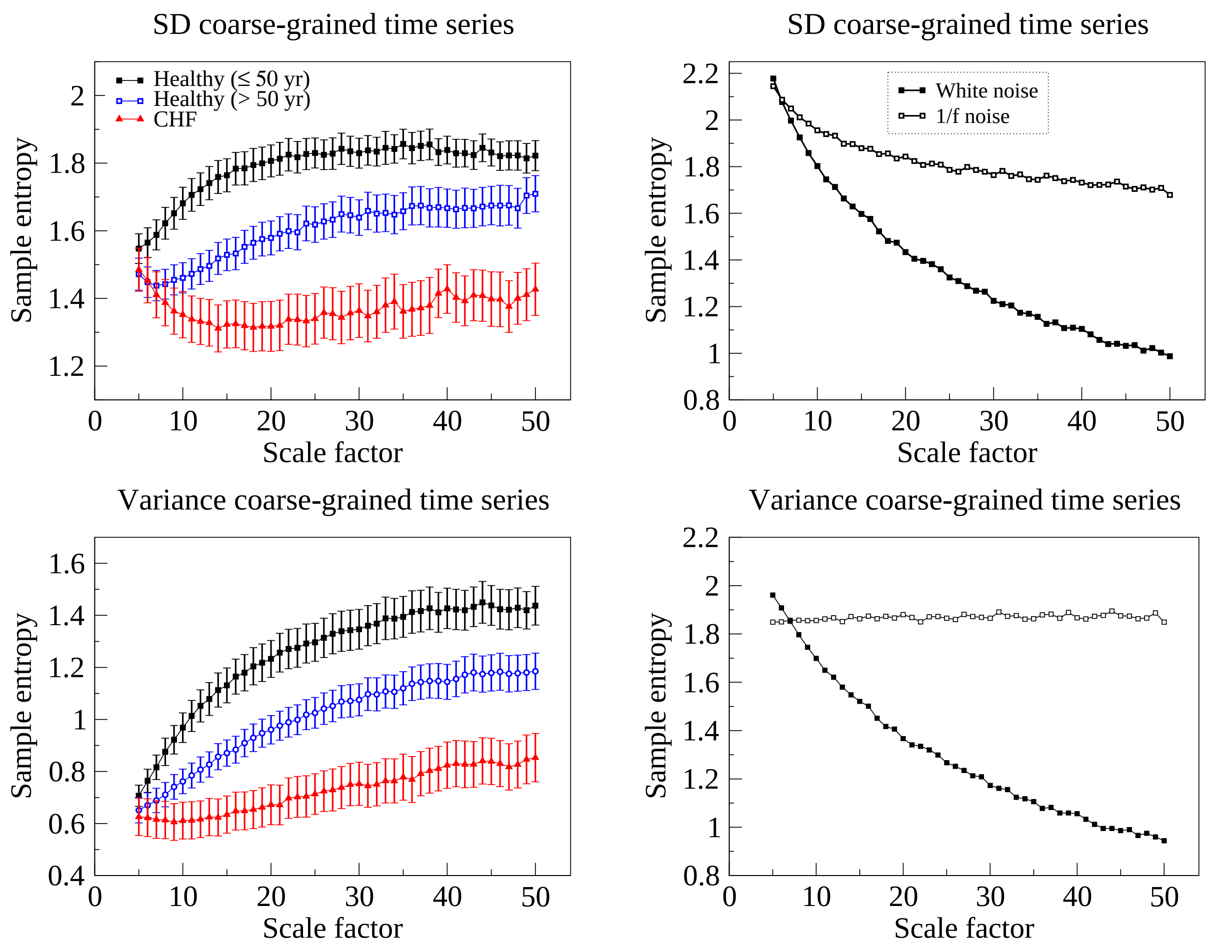


Figure 2: $\mathrm{MSE}_\sigma$ (top panels) and $\mathrm{MSE}_{\sigma^2}$ (bottom panels) analyses of RR interval time series (left panels) from healthy young to middle-aged ($\leq$ 50 years), healthy older ($>$ 50 years) subjects and patients with congestive (chronic) heart failure (CHF), and of simulated white and 1/f noise (right panels) time series. Symbols and error bars represent population mean and standard error values. The $r$ value was 20% of the SD of the C-G time series derived using a moving window comprising five data points (shortest scale). Physiologic and simulated time series comprised 50,000 and 131,072 ($2^{17}$) data points, respectively. The sample entropy parameter $m$ was 2.

## 2 Considerations regarding the selection of the parameter *r* for the calculation of sample entropy

In the sample entropy algorithm, the parameter $r$ is used to determine whether two data points, $x_i$ and $x_j$, are distinguishable or not. If $|x_i - x_j| \leq r$, then $x_i$ and $x_j$ are indistinguishable. Otherwise, they are "seen" as two different data points. In the $\mathrm{MSE}_\mu$ algorithm, the $r$ value is traditionally chosen as a percentage of the SD of the original time series, typically a value between 15 and 20%. An advantage of choosing $r$ in this way is the fact that two time series with different amplitudes but equal correlation properties are guaranteed to have the same sample entropy and the same MSE values. In fact, calculating sample entropy with an $r$ value that is a *percentage* of the time series' SD (e.g., 20%) is equivalent to calculating sample entropy with a *fixed* $r$ value (0.2) of a previously normalized time series.

An important observation regarding the choice of $r$ as a percentage of a time series' SD is the fact that two RR interval data points, e.g., 625 and 633 ms, may be indistinguishable when analyzing a given time series and distinguishable when analyzing another one. Consider the time series A and B with SDs of 38 ms and 42 ms, respectively. If $r$ = 20% of the time series' SD, then $r$ = 7.6 ms and $r$ = 8.4 ms, for A and B, respectively. Therefore, in one case, the RR intervals 625 and 633 ms are "seen" as different (since $|625 - 633| = 8.0 > 7.6$), and in the other case, as indistinguishable, i.e., below the accepted level of noise (since $|625 - 633| < 8.4$). If one is interested in quantifying entropy of two time series at the same level of "resolution," then one should choose a *fixed* (i.e., not dependent on SD) $r$ value. However, in doing so, the following consideration should be kept in mind.

Let us consider two time series $A$ and $B$ taking values from the sets $\{a, b\}$ and $\{a, b, c\}$, respectively. Assume that both time series are uncorrelated noise. For time series $A$, the probabilities of $a$ and $b$ are both 1/2; and for time series $B$, the probabilities of $a$, $b$ and $c$ are 1/3. To simplify the presentation, here we use Shannon entropy. For time series $A$, the entropy is:

$$-p(a)\ln[p(a)] - p(b)\ln[p(b)] = -2 \cdot 1/2 \cdot \ln(1/2) = -\ln(1/2)$$

For time series $B$, the entropy is:

$$-p(a)\ln[p(a)] - p(b)\ln[p(b)] - p(c)\ln[p(c)] = -3 \cdot 1/3 \cdot \ln(1/3) = -\ln(1/3)$$

The entropy for time series $A$ is smaller than for time series $B$ simply because the size of the alphabet of time series $A$ is smaller (two symbols, $a$ and $b$) than that of time series $B$ (three symbols, $a$, $b$ and $c$).

In conclusion, time series with a larger alphabet are more entropic than those with a smaller alphabet and identical correlation properties. Thus, when analyzing RR intervals time series with a fixed $r$ value, if one finds that a given time series is more entropic than another, one cannot be sure what the source of the difference is. Observed differences in entropy could be due to differences in the degree of randomness of the time series, differences in their range of values (larger/smaller alphabets) or a combination of the two.

Note that the two approaches discussed for choosing the $r$ value are both justifiable since they provide complementary information.

Our first application of MSE using a fixed $r$ value was in a project whose objective was to help forecast the need for lifesaving interventions based solely on 15-min ECG signals: Cancio LC, Batchinsky AI, Baker WL, et al. Combat casualties undergoing lifesaving interventions have decreased heart rate complexity at multiple time scales. J Crit Care. 2013;28(6):1093-8.

In most studies employing $\text{MSE}_\mu$, the $r$ value is set to a percentage of the SD of the C-G time series for the smallest scale included in the analysis. Typically, the smallest scale is scale one. Thus, the $r$ value is a percentage of the original time series' SD. This $r$ value is then used to calculate the sample entropy for all other C-G time series. A similar approach is also recommended for $\text{MSE}_\sigma$, $\text{MSE}_{\sigma^2}$ and $\text{MSE}_{MAD}$. However, in these cases, the first scale to be analyzed is not scale one. Typically, one would choose to start at scale five or above since the coarse-graining with windows with fewer than five data points may not retain important information pertaining to the degree of local volatility.

The results presented in Figure 2 for both SD and variance C-G time series follow this approach: $r$ is 20% of the SD of the C-G time series for scale 5.

$\text{MSE}_\sigma$, $\text{MSE}_{\sigma^2}$ and $\text{MSE}_{MAD}$ analyses can also we performed using an $r$ value that is a percentage of the original time series' SD. However, for the analysis of RR intervals time series, a value around 20% is not adequate. Instead, values below 1% are likely more suitable. We illustrate the issue using the RR interval time series shown in Fig. 1. The SD of this time series is 0.133 s. Twenty percent of this value is 0.027 s. Two data points are distinguishable if the difference between them is larger than 0.027 s. Consider, the SD C-G time series for scale 5 and select its median value, 0.0255 s. Only 14% of the data points in this SD C-G time series satisfy the condition: $|x_i - 0.0255| > 0.027$. In summary, the $r$ value derived from the original time series and used for the analysis of SD C-G time series is so large that 86% of the points around the SD C-G median value are indistinguishable.

Independent of which approach one chooses to follow ($r$ as a percentage of the CG time series for the first scale analyzed or as a fixed value), an important consideration is whether or not the chosen $r$ value is too restrictive or not restrictive enough. The GMSE algorithm outputs the number of matches with $m$ and $m + 1$ components. As a "rule of thumb," if the number of matches is less than 50 for the largest scale analyzed, then the $r$ value should be increased.

# 3 MSE$_\mu$ and MSE$_{MAD}$ analysis of RR interval time series from healthy young and older individuals and patients with CHF using a fixed $r$ value

We show the MSE analysis (Fig. 3) of RR interval time series using i) the mean and ii) the mean absolute deviation ($MAD = \sum |x_i - \bar{x}|/N$) metrics for coarse-graining the time series. The parameter $r$ is fixed at 8 ms. (The mean absolute difference is another measure of local variability.) The results indicate that healthy young subjects have the highest dynamical complexity, when considering both fluctuations in the mean and the mean absolute deviation (dispersion). The degrees of separation among the groups obtained with MSE$_\mu$ and MSE$_{MAD}$ are qualitatively comparable. (The area under the curve (AUC) of younger versus older is 0.85 and 0.88 for MSE$_\mu$ and MSE$_{MAD}$, respectively. The AUC of healthy older individual versus patients with CHF is 0.85 and 0.90 for MSE$_\mu$ and MSE$_{MAD}$, respectively.

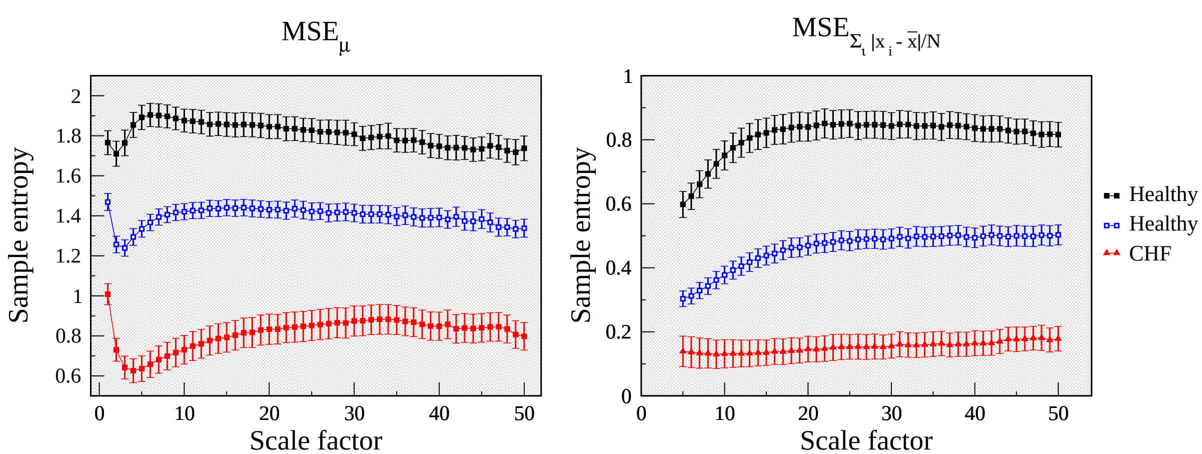


Figure 3: MSE analysis of mean (left) and absolute mean deviation (right) RR interval time series from healthy young and older subjects and patients with congestive heart failure, using a fixed $r$ (8 ms) value. The sample entropy parameter $m$ was 2. Time series length was 50,000 data points.

# 4 Effects of long-term trends and outliers on $MSE_\mu$ and $MSE_\sigma$ analyses

Long-term trends change the overall but not the local SD/variance of a time series. As a consequence trends affect mostly $MSE_\mu$ not $MSE_\sigma$ when the $r$ value is calculated as a percentage of the time series' SD. $MSE_\mu$ and $MSE_\sigma$ values are much less effected by trends in implementations that use a fixed $r$ value.

Figure 4 illustrates the effects that linear trends superimposed on normalized 1/f noise fluctuations have on $MSE_\mu$ and $MSE_\sigma$ values. We considered trends obtained by the concatenation of two linear segments. In one case (red line) the values of the function increase linearly between 4 and 8 for the first 30,000 and then decrease linearly from 8 to to 4 over the following 20,000 data points. In the other case (green line), the rates of increase/decrease were doubled. The superimposition of each of these trends on a 1/f noise time series resulted in signals A and B shown on the first and second panels, respectively.

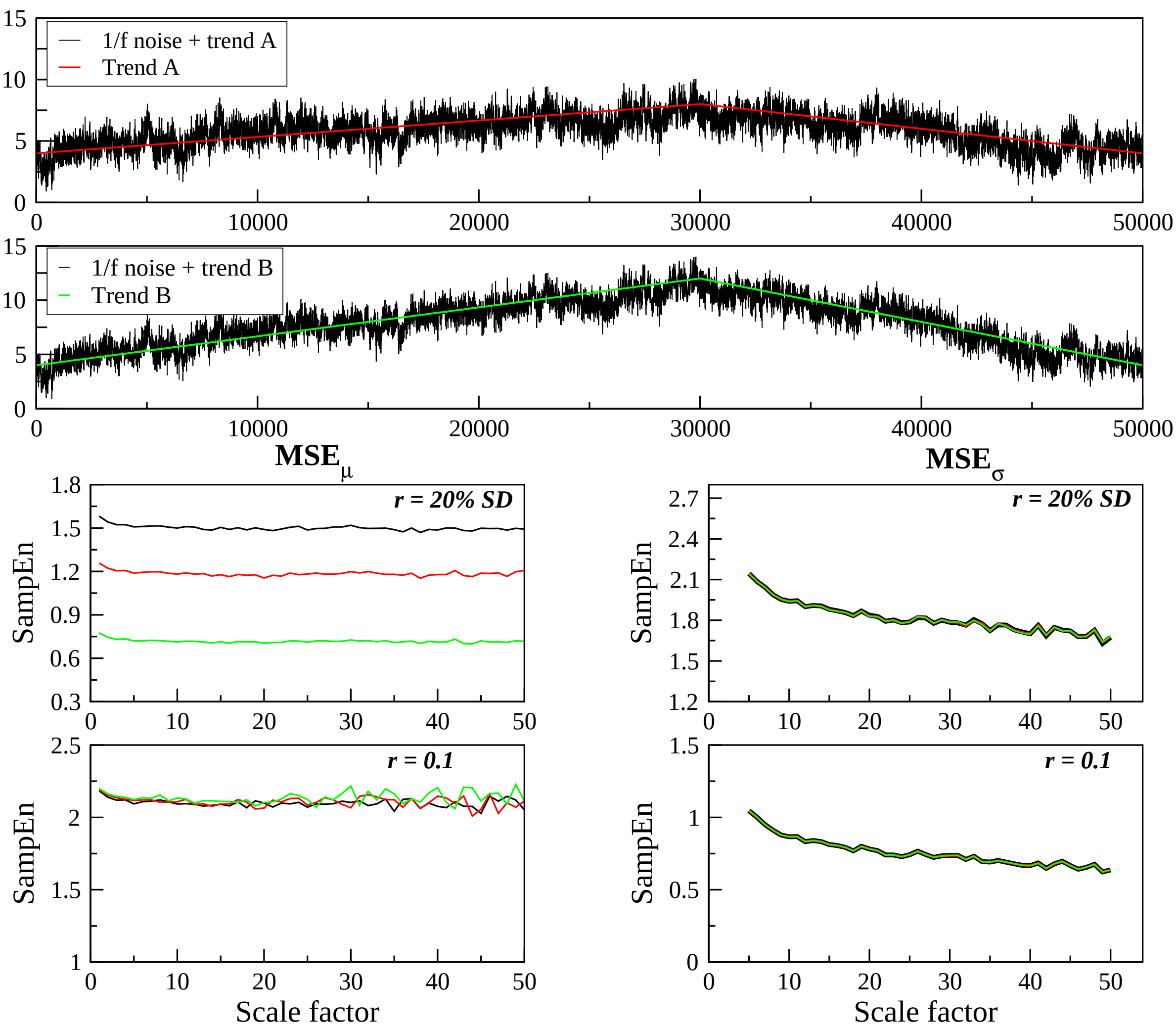


Figure 4: Effects of long-term trend on $MSE_\mu$ and $MSE_\sigma$ analyses of simulated 1/f noise time series, using variable and fixed $r$ values.

The SD of the original 1/f noise time series is one. The SDs of time series A and B are 1.3 (30% larger than the SD of the original series) and 2.3 (130% larger than the SD of the original series), respectively.

In MSE$_\mu$ analyses using the 20% of SD criterion, the absolute values of $r$ are 0.2, 0.26 and 0.46 for the original, time series A and B, respectively. The increase in the absolute value of $r$ due to the trends results in a higher number of matches and consequently in lower entropy values. Specifically, for scale 1, in the case of 1/f noise, the number of matches with $m$ = 2 and $m$ = 3 were 28,348,070 and 5,827,479, respectively. For time series A (B), the number of matches with $m$ = 2 and $m$ = 3 were 38,606,695 (60,511,987) and 10,973,294 (27,887,816), respectively. The effects of trends on MSE$_\mu$ can be obviated by using a fixed $r$ value. However, when using $r$ = 20% of SD, a barely noticeable trend can significantly change the values of entropy.

In MSE$_\sigma$ analysis, the $r$ value is a percentage of the SD of the SD coarse-grained time series obtained with a window of 5 data points. Since the slow trend has only a small effect on the SD coarse-grained time series, the changes in the entropy values are negligible.

Figure 5 shows the results of MSE$_\mu$ and MSE$_\sigma$ analyses of the RR interval time series from the groups of healthy young and older subjects and patients with CHF, using $r$ = 20% SD. The first 50,000 data points of each recording ($\approx$ 14-hours) were selected for analysis independent of the starting time (not available in most of these cases). As such, the time series may include both awake and sleep periods.

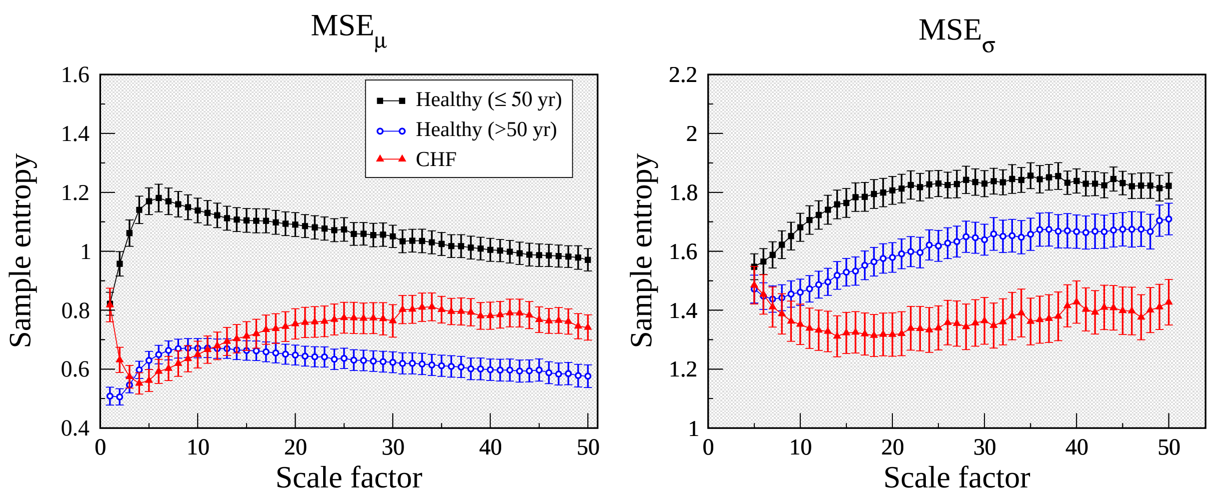


Figure 5: MSE$_\mu$ and MSE$_\sigma$ analyses of RR interval time series from healthy young and older subjects and patients with congestive heart failure, using $r$ = 20% SD. The sample entropy parameter m was 2. Time series length was 50,000 data points.

Healthy individuals are more likely to have more pronounced circadian variations than patients with CHF. Thus, the RR interval time series from the former group are more likely to exhibit trends of higher amplitude than the latter. These trends can justify the apparent contradictory MSE$_\mu$ results that indicate higher dynamical complexity for the CHF than the healthy older group. Such a conjecture is supported by the MSE$_\mu$ results obtained using a fixed $r$ value as well as the those of MSE$_\sigma$ analyses using both fixed and variable $r$ values. These findings highlight the need to analyze the data using different approaches in order to gain a deeper understanding of the properties of the dynamics and minimize the impact of known and unsuspected confounders.

The presence of outliers can also significantly affect MSE$_\sigma$, MSE$_{\sigma^2}$ and MSE$_{MAD}$ analyses. For this reason it is important to filter the time series prior to performing these analyses. The results presented here of the RR interval time series analyses were obtained using the filter described below. Alternatively, the use of a metric such as median absolute deviation for coarse-graining (not implemented here) could be considered.

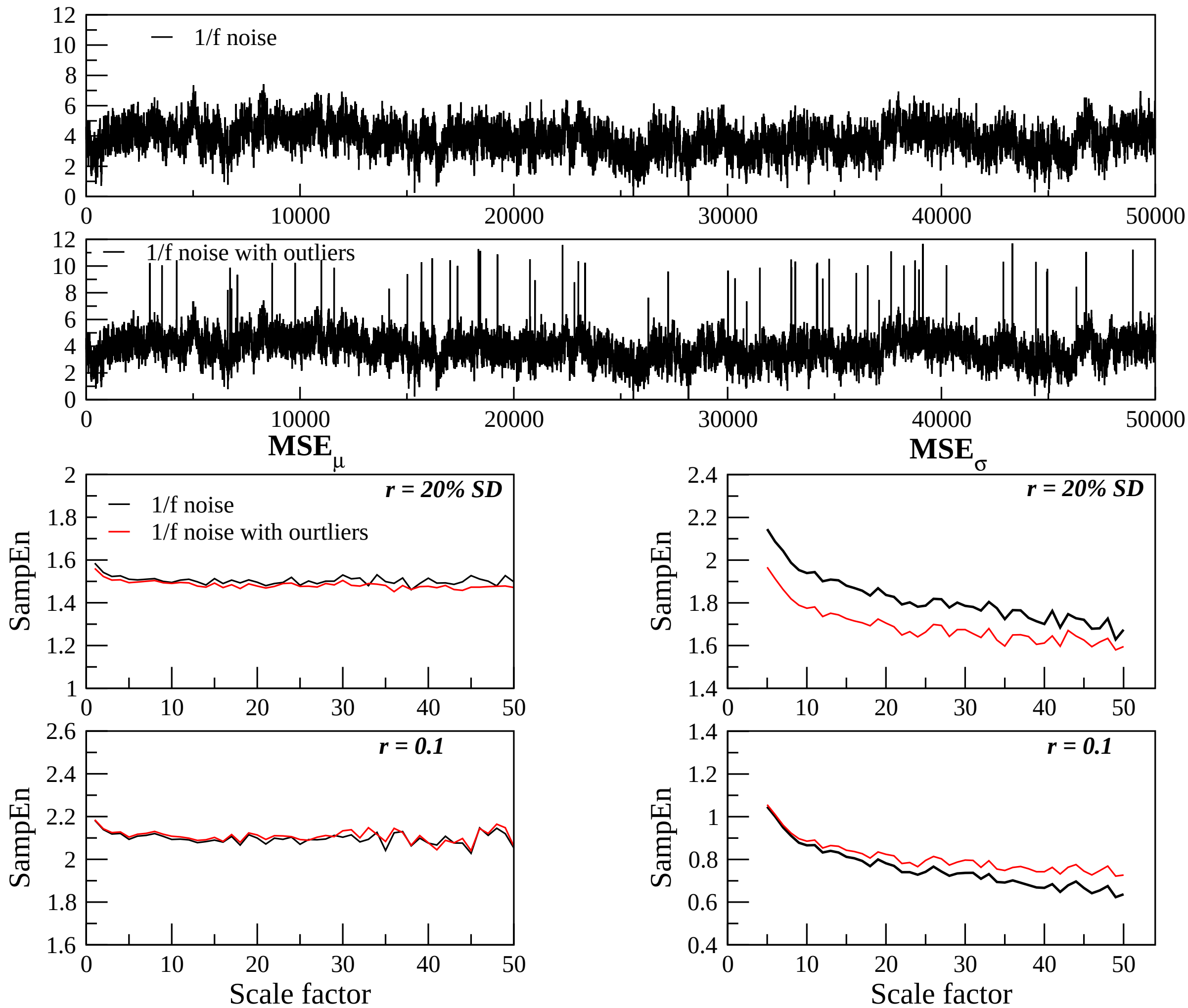


Figure 6: Effects of outliers on MSE$_\mu$ and MSE$_\sigma$ analyses of simulated 1/f noise time series.

# 5 Software for GMSE analysis

Download gmse.c, the C language source for a program that performs multiscale entropy analysis. The program can be compiled using any ANSI/ISO C compiler, and should be linked to the C math library (it uses only the sqrt function from that library). For example, using the freely available GNU C compiler, mse.c can be compiled into an executable mse by the command:

```
gcc -o gmse -O gmse.c -lm
```

## Preparing data for GMSE analysis

The program to compute GMSE processes text formatted input files with either one or two columns. Files with one column can be a list of RR intervals or any time series of interest. Files with two columns should be the time of occurrence of an R wave, $t(i)$, and the corresponding RR intervals, $t(i+1)-t(i)$. This type of RR interval file can be obtained from a beat annotation file using ann2rr:

```
ann2rr -r nsrdb/16265 -a atr -c -p N -P N  -i s3  -V s3 > 16265.RR
```

Example of a two-column input file (16265.RR):

| $t(i)$ | $RR(i) = t(i+1) - t(i)$ |
|---|---|
| 0.406 | 0.602 |
| 1.008 | 0.609 |
| 1.617 | 0.602 |
| 2.219 | 0.625 |
| 2.844 | 0.609 |
| 3.453 | 0.625 |
| 4.078 | 0.594 |
| 4.672 | 0.602 |
| ⋮ | ⋮ |
| 300.914 | 0.547 |
| 301.461 | 0.539 |
| 302.539 | 0.547 |
| 303.086 | 0.539 |
| ⋮ | ⋮ |

The two-column file, 16265.RR can be filtered using filt from the HRV Toolkit:

```
filt 0.3 20 -x 0.3 2.0
```

In this example, all points below 0.3 and above 2.0 are first removed. Next, to decide one whether the data point $x_i$ should be filtered out or kept, the mean value of the 20 data points to the left and the 20 data points to the right is calculated. The central point $x_i$ is deleted if it is below of above 30% (0.3) of the computed average value. The process is repeated for all data points.

When given two column input files (time and RR intervals), the GMSE program excludes RR intervals that are not consecutive. In the example above, there is an interruption in the time series between 301.461 and 302.539 s (values highlighted in yellow): $302.539 - 301.461 = 1.078 \neq 0.539$. Thus, the RR interval 0.539 will be excluded from the analysis. In addition, no vectors comprising the intervals immediately preceding (0.547) and following (0.547) the interruption will be considered.

## Summary of options and default values for GMSE

**–n:** largest scale. Default: 20.

**–a:** difference between consecutive scales. Default: 1.

**–c:** coarse-graining method: 1) mean; 2) standard deviation (SD); 3) variance; 4) mean absolute deviation. Default: SD.

**–x:** sample entropy noise tolerance value: fixed. Two data points, $u_i$, $u_j$ match if $|u_i - u_j| \leq x$

**–r:** sample entropy noise tolerance value: a number between 0 and 1 that represents a percent. Two data points, $u_i$, $u_j$ match if $|u_i - u_j| \leq r * SD$. Default: $r$ = 0.15. For mean coarse-graining analysis (traditional MSE), SD is the standard deviation of the original (scale 1) time series. For all other cases, SD is the standard deviation of scale 4 (default) coarse-grained time series.

**–m:** sample entropy vector length. Default: $m$ = 2.

**–i:** starting data point. Default: 0.

**–I:** ending data point. Default: end of file.

## Examples of command lines

1. `gmse -i 0 -I 50000 -c 1 < 16265.RR-filt > output`

   Coarse-graining method: mean (traditional MSE). Sample entropy parameters values $m$ = 2, $r$ = 0.15 (15% of SD of the original time series). The first 50,000 data points are considered.

   The output values are:

| Scale | SampEn | $m_3/m_2$ | $r * SD$ |
|---|---|---|---|
| 1 | 1.1897 | 7253987/23837718 | 0.013203 |
| 2 | 1.3032 | 1600494/5891466 | 0.013203 |
| 3 | 1.4956 | 473897/2114637 | 0.013203 |
| 4 | 1.6527 | 179051/934800 | 0.013203 |
| 5 | 1.6506 | 117176/610500 | 0.013203 |
| 6 | 1.6294 | 85533/436301 | 0.013203 |
| 7 | 1.6505 | 57324/298632 | 0.013203 |
| 8 | 1.6164 | 47163/237466 | 0.013203 |
| 9 | 1.5821 | 40749/198244 | 0.013203 |
| 10 | 1.5895 | 31764/155689 | 0.013203 |
| 11 | 1.5332 | 28626/132628 | 0.013203 |
| 12 | 1.5297 | 24666/113877 | 0.013203 |
| 13 | 1.5189 | 21291/97245 | 0.013203 |
| 14 | 1.4899 | 18804/83427 | 0.013203 |
| 15 | 1.4710 | 16822/73235 | 0.013203 |
| 16 | 1.4687 | 14703/63866 | 0.013203 |
| 17 | 1.4734 | 12977/56633 | 0.013203 |
| 18 | 1.4482 | 11873/50527 | 0.013203 |
| 19 | 1.4621 | 9992/43114 | 0.013203 |
| 20 | 1.4319 | 9591/40155 | 0.013203 |

2. `gmse -i 0 -I 50000 -r 0.2 -c 2 < 16265.RR-filt > output`

   Coarse-graining method: SD. Sample entropy parameters $m$ = 2, $r$ = 0.20 (20% of the coarse-grained time series for scale 5). This is the command line used to derive the results shown on the left panel of Fig. 2 and on the right panel of Fig. 5.

   The output values are:

| Scale | SampEn | $m_3/m_2$ | $r * SD$ |
|---|---|---|---|
| 5 | 1.4648 | 307814/1331797 | 0.003835 |
| 6 | 1.5233 | 168245/771816 | 0.003835 |
| 7 | 1.5829 | 99565/484806 | 0.003835 |
| 8 | 1.6365 | 62961/323456 | 0.003835 |
| 9 | 1.7058 | 40966/225554 | 0.003835 |
| 10 | 1.7258 | 30256/169946 | 0.003835 |
| 11 | 1.7605 | 21967/127745 | 0.003835 |
| 12 | 1.8010 | 16915/102437 | 0.003835 |
| 13 | 1.8103 | 13668/83541 | 0.003835 |
| 14 | 1.8485 | 10580/67189 | 0.003835 |
| 15 | 1.8309 | 9132/56979 | 0.003835 |
| 16 | 1.8727 | 7565/49216 | 0.003835 |
| 17 | 1.8786 | 6460/42275 | 0.003835 |
| 18 | 1.8836 | 5632/37041 | 0.003835 |
| 19 | 1.8833 | 4867/32000 | 0.003835 |
| 20 | 1.9080 | 4180/28171 | 0.003835 |

3. `gmse -i 0 -I 50000 -x 0.008 -c 4 < 16265.RR-filt > output`

   Mean absolute deviation is the chosen metric for coarse-graining. Sample entropy parameters $m$ = 2, $r$ = 0.008 (fixed, not a % of SD). This is the command line used to derive the results plotted on the right side panel of Fig. 3.

   The output values are:

| Scale | SampEn | $m_3/m_2$ | $r * SD$ |
|---|---|---|---|
| 5 | 0.7032 | 3594655/7261796 | 0.008000 |
| 6 | 0.7591 | 2008629/4291038 | 0.008000 |
| 7 | 0.8139 | 1186303/2677237 | 0.008000 |
| 8 | 0.8624 | 767179/1817262 | 0.008000 |
| 9 | 0.9165 | 506521/1266507 | 0.008000 |
| 10 | 0.9311 | 380264/964870 | 0.008000 |
| 11 | 0.9756 | 273555/725658 | 0.008000 |
| 12 | 0.9891 | 217627/585165 | 0.008000 |
| 13 | 0.9915 | 177947/479594 | 0.008000 |
| 14 | 1.0232 | 140291/390320 | 0.008000 |
| 15 | 1.0296 | 117161/328049 | 0.008000 |
| 16 | 1.0236 | 104222/290078 | 0.008000 |
| 17 | 1.0395 | 89258/252412 | 0.008000 |
| 18 | 1.0468 | 77024/219414 | 0.008000 |
| 19 | 1.0332 | 68169/191564 | 0.008000 |
| 20 | 1.0375 | 60541/170863 | 0.008000 |

# Selected Bibliography


[1] Costa M, Goldberger AL, Peng C-K. Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett* 2002;89:68102.

[2] Costa M, Goldberger AL, Peng C-K. Multiscale entropy analysis of biological signal. *Phys Rev E* 2005;71:021906.

[3] Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol.* 2000;278:H2039-49.

[4] Costa MD, Goldberger AL. Generalized multiscale entropy analysis: Application to quantifying the complex volatility of human heartbeat time series. *Entropy* 2015;17:1197-203.

[5] Cancio LC, Batchinsky AI, Baker WL, Necsoiu C, Salinas J, Goldberger AL, Costa MD. Combat casualties undergoing lifesaving interventions have decreased heart rate complexity at multiple time scales. *J Crit Care* 2013;28:1093-8.