Physiological time-series analysis using approximate entropy and sample entropy

JOSHUA S. RICHMAN,1,2 AND J. RANDALL MOORMAN3
1Cardiovascular Division, Department of Internal Medicine, and Department of Molecular Physiology and Biological Physics, and Cardiovascular Research Center, University of Virginia Health Sciences Center, Charlottesville, Virginia 22908; and 2Medical Automation Systems, Charlottesville, Virginia 22903

Richman, Joshua S., and J. Randall Moorman. Physiological time-series analysis using approximate and sample entropy. Am J Physiol Heart Circ Physiol 278: H2039–H2049, 2000.—Entropy, as it relates to dynamical systems, is the rate of information production. Methods for estimation of the entropy of a system represented by a time series are not, however, well suited to analysis of the short and noisy data sets encountered in cardiovascular and other biological studies. Pincus introduced approximate entropy (ApEn), a set of measures of system complexity closely related to entropy, which is easily applied to clinical cardiovascular and other time series. ApEn statistics, however, lead to inconsistent results. We have developed a new and related complexity measure, sample entropy (SampEn), and have compared ApEn and SampEn by using them to analyze sets of random numbers with known probabilistic character. We have also evaluated cross-ApEn and cross-SampEn, which use cardiovascular data sets to measure the similarity of two distinct time series. SampEn agreed with theory much more closely than ApEn over a broad range of conditions. The improved accuracy of SampEn statistics should make them useful in the study of experimental clinical cardiovascular and other biological time series.

other hand, is defined as long as one template finds a
match, and we find that cross-SampEn remains rela-
tively consistent for conditions where cross-ApEn does not.

**THEORY**

ApEn reports on similarity in time series. We employ the terminology and notation of Grassberger and Pro-
caccia (10), Eckmann and Ruelle (5), and Pincus (21) in
describing techniques for estimating the Kolmogorov
entropy of a process represented by a time series and the
related statistics ApEn and SampEn. The param-
eters N, m, and r must be fixed for each calculation. N
is the length of the time series, m is the length of
sequences to be compared, and r is the tolerance for
accepting matches. It is convenient to set the tolerance
as \( r \times SD \), the standard deviation of the data set,
allowing measurements on data sets with different
amplitudes to be compared. Throughout this work, all
time series have been normalized to have SD = 1.

We proceed as follows: For a time series of N points,
\( \{ u(j) \} : 1 \leq j \leq N \) forms the \( N \) \( m \) \( 1 \) vectors \( x_m(i) \) for
\( 1 \leq i \leq N \) \( m \) 1, where \( x_m(i) = u(i + k) \):
0 \( k \leq m \) 1 \( m \) is the vector of \( m \) data points from \( u(i) \)
to \( u(i + m - 1) \). The distance between two such vectors
is defined to be \( d(x(i), x(j)) = \max | u(i + k) - u(j + k) |: 0 \leq k \leq m \) 1 \( m \), the maximum difference of their corre-
spending scalar components. Let \( B_i \) be the number of
vectors \( x_m(i) \) within \( r \) of \( x_m(i) \) and let \( A_i \) be the number of
vectors \( x_m(i) \) within \( r \) of \( x_m(i) \). Define the function \( C^{(m)}(r)(= (B_i) / (N - m + 1) \) in calculating \( C^{(m)}(r) \),
the vector \( x_m(i) \) is called the template, and an instance
where a vector \( x_m(i) \) is within \( r \) of it is called a template
match. \( C^{(m)}(r) \) is the probability that any vector \( x_m(i) \) is
within \( r \) of \( x_m(i) \). The function \( \phi^{(m)}(r) = (N - m + 1) \)
\( \sum_{i=1}^{m-1} \) Int[C^{(m)}(r)] is the average of the natural lo-
garithms of the functions \( C^{(m)}(r) \). Eckmann and Ruelle (5)
suggest approximating the entropy of the underlying
process as \( \lim_{m \to \infty} \lim_{N \to \infty} \lim_{r \to 0} [ \phi^{(m)}(r) - \phi^{(m+1)}(r) ] \).
Because of these limits, this definition is not suited to
the analysis of the finite and noisy time series derived
from experiments.

Pincus (21) saw that the calculation of \( \phi^{(m)}(r) -
\phi^{(m+1)}(r) \) for fixed parameters m, r, and N had
intrinsic interest as a measure of regularity and complexity.
He defines the related parameter ApEn(m, r, N) = \( \lim_{m \to \infty} \phi^{(m)}(r) - \phi^{(m+1)}(r) \), which for finite data sets is
estimated by the statistic \( \text{ApEn}(m, r, N) = (N - m + 1) \)
\( \sum_{i=1}^{m-1} \) Int[C^{(m)}(r)] - \( (N - m) \) \( \sum_{i=1}^{m-1} \) Int[C^{(m-1)}(r)].
Algebraic manipulation reveals that \( \text{ApEn}(m, r, N) = (N - m + 1) \)
\( \sum_{i=1}^{m-1} \) Int[C^{(m)}(r)] - \( (N - m) \) \( \sum_{i=1}^{m-1} \) Int[C^{(m-1)}(r)].
When \( N \) is large, ApEn(m, r, N) is approxi-
mately equal to \( (N - m + 1) \) \( \sum_{i=1}^{m-1} \) [\( - \ln (A_i/B_i) \)], the aver-
age over \( i \) of the negative natural logarithm of the con-
ditional probability that \( d(x_{m+1}(i), x_{m+1}(j)) \) \( \leq r \)
given that \( d(x_m(i), x_m(j)) \) \( \leq r \). The difference between
ApEn(m, r, N) and this average logarithmic proba-
bility is less than \( (N - m + 1) \) \( \sum_{i=1}^{m-1} \) \( - \ln (A_i/B_i) \), which is
<0.05 for \( N - m + 1 \geq 90 \) and <0.02 for \( N - m + 1 \geq 283 \). They differ because there are \( N - m + 1 \) templates
of length \( m \), but only \( N - m \) templates of length \( m + 1 \)
(27). Thus, although the quantity \( C^{(m+1)}(r) \) is defined,
\( C^{(m+1)}(r) \) is not, simply because the vector \( u_{m+1}(N - m + 1) \) does not exist. For practical pu-
rposes, ApEn can be thought of as the negative natural
logarithm of the probability that sequences that are
close for \( m \) points remain close for an additional point.
Because conditional probabilities lie between 0 and 1,
the parameter ApEn(m, r, N) is a positive number of
infinite range. For finite \( N \), however, the largest pos-
sible value of ApEn(m, r, N) is \( -\ln (N - m) \) \( -\ln (N - m - 1) \), so ApEn(m, r, N) \( \leq \ln (N - m) \).

ApEn(m, r, N) is biased and suggests more similarity
than is present. It is important to note that ApEn takes
a template-wise approach to calculating this average
logarithmic probability, first calculating a probability
for each template. The ApEn algorithm thus requires
that each template contribute a defined, nonzero prob-
ability. This constraint is overcome by allowing each
template to match itself, a practice we will refer to
as self-matching. This ensures that the functions \( C^{(m)}(r) \)
are >0 for all \( i \), thereby avoiding the occurrence of
\( \ln (0) \) in the calculation. Thus ApEn(m, r, N) is certain
to be defined under all circumstances. Pincus and
Goldberger (23, 27) note that, as a consequence of this
practice, ApEn(m, r, N) is a biased statistic. Formally,
a statistic is biased if its expected value is not equal to
the parameter it estimates. ApEn statistics are biased,
because the expected value of ApEn(m, r, N) is less than
the parameter ApEn(m, r) (27).

To discuss the bias caused by including self-matches,
let us redefine the conditional probability associated
with the template \( x_m(i) \) by letting \( B_i \) denote the number
of vectors \( x_m(i) \) with \( j \neq i \), such that \( d(x_{m+1}(i), x_{m+1}(j)) \) \( \leq r \) by \( A_i \). The ApEn algorithm thus assigns to
the template \( x_m(i) \) a biased conditional probability of
\( (A_i + 1)/(B_i + 1) \), which is always greater than the
unbiased \( A_i/B_i \). In the limit as \( N \) approaches infinity, \( A_i \)
and \( B_i \) will generally be large, making the biased and
unbiased probabilities asymptotically equivalent. There-
fore, this bias is evident only for the analysis of finite
data sets and is a characteristic of the statistic
ApEn(m, r, N), rather than the parameter ApEn(m, r).
For a finite \( N \), however, the result is that ApEn(m, r, N)
is biased toward lower values of ApEn and returns
values below those predicted by theory.

The largest deviation occurs when a large proportion
of templates have \( B_i = A_i = 0 \), since these templates are
assigned a conditional probability of 1, corresponding
to perfect order. Furthermore, the difference between
the biased and unbiased conditional probabilities as-
signed to individual templates makes the calculation
sensitive to record length in a way that depends on the
conditional probability. Suppose that the unbiased con-
ditional probability is known and denote it by CP. For a
given \( u_m(i) \) let \( B_i \) denote the number of template
matches without counting self-matches. The original
algorithm estimates CP as \( (1 + A_i)/(1 + B_i) \) =
\( (1 + B_i \times CP)/(1 + B_i) \). The fractional error of this

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relative to CP is \( \text{Err} = [(1 + B_i \times CP)/(1 + B_i)] - CP/CP \). To find the value of \( B_i \) necessary to keep the fractional error below a threshold \( \text{Err}_{\text{max}} \) we isolate \( B_i \) from the inequality \( \text{Err} \leq \text{Err}_{\text{max}} \), yielding \( B_i \approx [1 - CP/(\text{Err}_{\text{max}} + 1)]/(CP \times \text{Err}_{\text{max}}) \). For independent, identically distributed (iid) random numbers, obtaining \( B_i \) matches of length \( m \) requires a data set containing, on average, \( B_i/(CP)^m \) templates. For iid random numbers and \( m = 2 \), estimating \( CP = 0.368 \) \([\text{ApEn}(r, N) = 1]\) within \( \text{Err}_{\text{max}} = 0.05 \) requires \( B_i \approx 33 \) and a data set of \( >240 \) points. Estimating \( CP = 0.135 \) \([\text{ApEn}(m, r, N) = 2]\) with similar resolution requires \( B_i \approx 127 \) and \( >6,900 \) points.

The most straightforward way to eliminate the bias would be to remove self-matching from the \( \text{ApEn} \) algorithm, leaving it otherwise unaltered. However, without the inclusion of self-matches, the \( \text{ApEn} \) algorithm is not defined unless \( C_{m-1}^{m-1}(r) > 0 \) for every \( r \). Removing self-matches would make \( \text{ApEn} \) statistics highly sensitive to outliers; if there were a single template that matched no other vector, \( \text{ApEn} \) could not be calculated because of the occurrence of \( \ln(0) \). For the set of uniform random numbers shown in Fig. 1a, without self-matches, \( \text{ApEn}(1, r, N) \) would not have been defined for \( r \leq 0.63 \) and \( N < 4,000 \); \( \text{ApEn}(2, r, N) \) would have required \( r \geq 1 \) for \( N < 4,000 \). Thus, for many practical applications, self-matches cannot simply be excluded when \( \text{ApEn} \) statistics are calculated.

Can the bias be corrected? It is suggested that this bias can be reduced with a family of estimators \( \epsilon \) by defining \( C_{m-1}^m(r) = (N - m + 1)^{-1} \sum_{i=0}^{N-m+1} C_{m-1}^i(r) \) and \( \text{ApEn}(m, r, N) = \Phi_{m-1}(r) - \Phi_{m-1}^1(r) \). For large \( N \), this is very close to estimating the conditional probabilities by \( (\epsilon + A_i)/(\epsilon + B_i) \). When \( \epsilon < 1 \), the error due to counting self-matches is reduced, but this algorithm would still report a conditional probability of 1 in the event that only self-matches are encountered. Another strategy would be to define \( \text{ApEn}_{\text{max}}(m, r, N) = \Phi_{m}^0(r) - \Phi_{m-1}^0(r) \) where \( \epsilon_1 \) and \( \epsilon_2 \) are small and \( \epsilon_1 < \epsilon_2 \). This is similar to estimating the conditional probabilities by \( (\epsilon_1 + A_i)/(\epsilon_2 + B_i) \).

A template reporting only self-matches would be assigned a probability of \( \epsilon_1/\epsilon_2 \). This remains a biased estimate of \( \text{ApEn} \), with bias toward \( -\ln(\epsilon_1/\epsilon_2) \) when a large proportion of templates report only self-matches. If \( \epsilon_1/\epsilon_2 = (N - m + 1)^{-1} \) and \( A_i = B_i = 0 \), the bias is toward the lowest observable probability. This is the opposite bias of the original formulation of \( \text{ApEn} \), where the bias is toward the highest possible probability. Still another approach would be to use the estimators \( \epsilon_1 \) and \( \epsilon_2 \) but incorporate them into the calculation only when \( A_i \) or \( B_i = 0 \), respectively. This would estimate the probabilities as \( A_i/B_i \) and would simply redefine \( A_i = \epsilon_1 \) when \( A_i = 0 \) and \( B_i = \epsilon_2 \) when \( B_i = 0 \). These approaches reduce the bias in the estimation of the individual conditional probabilities and ensure that perfect order would not be reported where none had been detected. None of the corrections eliminates bias; the bias is minimized only if \( \epsilon_1/\epsilon_2 = CP \), but \( CP \) is not known beforehand. Thus no family of estimators \( \epsilon \) that minimizes bias can be chosen a priori.

\( \text{SampEn} \) statistics have reduced bias. We developed \( \text{SampEn} \) statistics to be free of the bias caused by self-matching. The name refers to the applicability to time series data sampled from a continuous process. In addition, the algorithm suggests ways to employ sample statistics to evaluate the results, as explained below.

There are two major differences between \( \text{SampEn} \) and \( \text{ApEn} \) statistics. First, \( \text{SampEn} \) does not count self-matches. We justified discounting self-matches on the grounds that entropy is conceived as a measure of the rate of information production (5), and in this case, the algorithms are not designed to distinguish between random and deterministic behavior.
context comparing data with themselves is meaningless. Furthermore, self-matches are explicitly dismissed in the later work of Grassberger and co-workers (2, 9, 11). Second, SampEn does not use a template-wise approach when estimating conditional probabilities. To be defined, SampEn requires only that one template find a match of length $m + 1$.

We began from the work of Grassberger and Procaccia (10), who defined $C^m(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m} C^m_{i,r}$, the average of the $C^m_{i,r}$ defined above. This differs from $\Phi^m(r)$ only in that $\Phi^m(r)$ is the average of the natural logarithms of the $C^m_{i,r}$. They suggest approximating the Kolmogorov entropy of a process represented by a time series by $\lim_{m \to \infty} \lim_{N \to \infty} \text{lim}_{m \to \infty} \text{lim}_{N \to \infty} \text{lim}_{m \to \infty} \ln [C^{m+1}_r(C^m_r)]; \text{self-matches are counted, and} C^{m+1}_r(C^m_r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m} A_i/(N - m) \sigma_{N-m-1} B_j$.

In this form, however, the limits render it unsuitable for the analysis of finite time series with noise. We therefore made two alterations to adapt it to this purpose. First, we followed their later practice in calculating correlation integrals (2, 9, 11) and did not consider self-matches when computing $C^m(r)$. Second, we considered only the first $N - m$ vectors of length $m$, ensuring that, for $1 \leq i \leq N - m$, $x_m(i)$ and $x_{m+1}(i)$ were defined.

We defined $B^{m,r}(r)$ as $(N - m + 1)^{-1}$ times the number of vectors $x_m(j)$ within $r$ of $x_m(i)$, where $j$ ranges from 1 to $N - m$, and $j \neq i$ to exclude self-matches. We then defined $A^{m,r}(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m} B^{m,r}(r)$. Similarly, we defined $A^{m,r}_j(r)$ as $(N - m + 1)^{-1}$ times the number of vectors $x_{m+1}(j)$ within $r$ of $x_{m+1}(i)$, where $j$ ranges from 1 to $N - m$, and $j \neq i$, and set $A^{m,r}_j(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m} A^{m,r}_j(r)$. $B^{m,r}(r)$ is then the probability that two sequences will match for $m$ points, whereas $A^{m,r}_j(r)$ is the probability that two sequences will match for $m + 1$ points. We then defined the parameter SampEn($m, r$) = $\lim_{m \to \infty} \text{lim}_{N \to \infty} \text{lim}_{m \to \infty} \text{lim}_{N \to \infty} \text{lim}_{m \to \infty} \ln [A^{m,r}(r)/B^{m,r}(r)],$ which is estimated by the statistic SampEn($m, r, N$) = $\ln [A^{m,r}(r)/B^{m,r}(r)].$ Where there is no confusion about the parameter $r$ and the length $m$ of the template vector, we set $B = [(N - m - 1)(N - m)/2] B^{m,r}(r)$ and $A = [(N - m - 1)(N - m)/2] A^{m,r}(r)$, so that $B$ is the total number of template matches of length $m$ and $A$ is the total number of forward matches of length $m + 1$. We note that $A/B = [A^{m,r}(r)/B^{m,r}(r)]$, so SampEn($m, r, N$) can be expressed as $-\ln (A/B)$.

The quantity $A/B$ is precisely the conditional probability that two sequences within a tolerance $r$ for $m$ points remain within $r$ of each other at the next point. In contrast to ApEn($m, r, N$), which calculates probabilities in a template-wise fashion, SampEn($m, r, N$) calculates the negative logarithm of a probability associated with the time series as a whole. SampEn($m, r, N$) will be defined except when $B = 0$, in which case no regularity has been detected, or when $A = 0$, which corresponds to a conditional probability of 0 and an infinite value of SampEn($m, r, N$). The lowest nonzero conditional probability that this algorithm can report is $2(N - m - 1)(N - m)^{-1}$. Thus, the statistic SampEn($m, r, N$) has $\ln (N - m) + \ln (N - m - 1) - \ln (2)$ as an upper bound, nearly doubling $\ln (N - m)$, the dynamic range of ApEn($m, r, N$).

Confidence intervals inform the implementation of SampEn statistics. SampEn is not defined unless template and forward matches occur and is not necessarily reliable for small numbers of matches. We have reviewed SampEn($m, r, N$) calculation as a process of sampling information about regularity in the time series and used sample statistics to inform us of the reliability of the calculated result. For example, say that we find B template matches, allowing for no more than B forward matches, A of which actually occur. We assign a value of 1 to the A forward matches and a value of 0 to the (B - A) potential forward matches that do not occur and compute the conditional probability measured by SampEn as the average of this sample of Os and Is. For operational purposes, we will assume that the sample averages follow a Student's $t$ distribution, where $d$ is the number of degrees of freedom. We can then say with 95% confidence that the "true" average conditional probability of the process is within $SD_{B - 0.975}/A$ of the sample average, where $SD$ is the sample standard deviation and $t_{0.975}$ is the upper 2.5th percentile of a $t$ distribution with $B - 1$ degrees of freedom (31). The size of the confidence intervals depends on the number B and the number of forward matches. Informally, large confidence intervals around SampEn($m, r, N$) indicate that there are insufficient data to estimate the conditional probability with confidence for that choice of m and r. In addition, confidence intervals allow standard statistical tests of the significance of differences between data sets.

The confidence intervals for SampEn are displayed as error bars in the figures. For some small values of N and r, no value of SampEn is given. This indicates that B = 0, A = 0, or the confidence intervals extended to a probability of >1 or <0. In these cases, no value of SampEn($m, r, N$) can be assigned with confidence.

Cross-ApEn and cross-SampEn measure asynchrony. Cross-ApEn is a recently introduced technique for comparing two different time series to assess their degree of asynchrony or dissimilarity (20, 28). The definition of cross-ApEn is very similar to ApEn. Given two time series of N points $u(j): 1 \leq j \leq N$ and $v(j): 1 \leq j \leq N$, form the vectors $x_m(i) = [u(i + k): 0 \leq k \leq m - 1]$ and $y_m(i) = [v(i + k): 0 \leq k \leq m - 1]$. The distance between two such vectors is defined as $d[x_m(i), y_m(j)] = \max |u(i + k) - v(j + k)|: 0 \leq k \leq m - 1$. Define $C^m_r(v|u)$ as the number of $y_m(j)$ within $r$ of $x_m(i)$ divided by $(N - m + 1)$, then define $\Phi^m_r(v|u) = (N - m + 1)^{-1} \sum_{i=1}^{N-m} \ln [C^m_r(v|u)]$, and cross-ApEn($m, r, N$)($v|u$) = $\Phi^m_r(v|u) - \Phi^{m-1}_r(v|u)$. This is identical to the definition of the statistic ApEn, except the templates are chosen from the series u and compared with vectors from v. There is thus a directionality to this analysis, and we will call the series that contributes the templates the template series and the series with which they are compared the target series. We can then refer to cross-ApEn($m, r, N$) (target $|$ template).
We made two observations. First, because no template is compared with itself, there are no self-matches. Consequently, $C(n)(r)_{\{v\mid u\}}$ can equal 0, and there is no assurance that cross-ApEn($m$, $r$, $N$)($v\mid u$) will be defined. Second, there is a "direction dependence" of cross-ApEn analysis. We defined cross-SampEn to avoid both potential problems.

Cross-ApEn is not always defined. As noted above, cross-ApEn does not include self-matching and, thus, does not inherently suffer from the same bias as ApEn. A potential problem, however, remains in the necessity for each template to generate a defined, nonzero conditional probability. Thus each template must find at least one match for $m+1$ points, or a probability must be assigned to it. No guidelines have been suggested for handling this potential difficulty. Cross-SampEn, on the other hand, requires only that one pair of vectors in the two series match for $m+1$ points.

The family of MIX($P$) stochastic processes (21) provided a testing ground for cross-ApEn. Informally, the MIX($P$) time series of $N$ points, where $P$ is between 0 and 1, is a sine wave, where $N \times P$ randomly chosen points have been replaced with random noise. We calculated cross-ApEn($1$, $r$, $250$) for the pair $[\text{MIX}(Q)\mid \text{MIX}(P)]$ and its direction conjugate $[\text{MIX}(P)\mid \text{MIX}(Q)]$ for 16 realizations of each of the 6 combinations of $P = 0.1, 0.2, 0.3$ and $Q = 0.5, 0.7$ over a range of values of $r$ from 0.01 to 1.0. Cross-ApEn($1$, $r$, $250$) $[\text{MIX}(Q)\mid \text{MIX}(P)]$ was not defined for any of the 96 pairs for $r = 0.16$ and was defined for all of them only for $r \geq 0.50$. Cross-ApEn($1$, $r$, $250$) $[\text{MIX}(P)\mid \text{MIX}(Q)]$ was not defined for any values of $r = 0.32$ and was defined for all pairs only for $r = 1.0$.

To broaden the conditions for which cross-ApEn was defined, we introduced a correction factor into its algorithm. To avoid $\ln(0)$ whenever $C(n)(r)_{\{v\mid u\}} = 0$ or $C^{m-1}(r)_{\{v\mid u\}} = 0$, we redefined them to be positive and nonzero. Rather than include these factors into the calculation of each $C(n)(r)_{\{v\mid u\}}$ and $C^{m-1}(r)_{\{v\mid u\}}$, we minimized their impact on the overall calculation by including them only when needed to ensure that cross-ApEn is defined. The cost of this adjustment, however, is the introduction of bias. For this reason, we tested cross-ApEn with two different correction strategies. The first strategy, which we called bias 0, was very similar to self-matching; we simply set any $C(n)(r)_{\{v\mid u\}}$ or $C^{m-1}(r)_{\{v\mid u\}} = 1$ if it would otherwise have been 0. Thus, if a template matched no other at all, it would be assigned a conditional probability of 1, as with the original description of ApEn. If, however, $C(n)(r)_{\{v\mid u\}} \neq 0$ but $C^{m-1}(r)_{\{v\mid u\}} = 0$, we redefined $C^{m-1}(r)_{\{v\mid u\}} = (N - m)^{-1}$, so that the probability assigned would be the lowest observable, nonzero probability given the nonzero value of $C(n)(r)_{\{v\mid u\}}$.

The second approach, which we called bias max, also only modified the functions $C(n)(r)_{\{v\mid u\}}$ and $C^{m-1}(r)_{\{v\mid u\}}$ that would otherwise have been 0. Here, $C(n)(r)_{\{v\mid u\}}$ was redefined to be 1 when it would otherwise have been 0 and $C^{m-1}(r)_{\{v\mid u\}}$ was redefined to be $(N - m + 1)^{-1}$, as for bias 0.

The only difference between the two strategies is that bias max assigns to a template yielding no matches at all a probability of $(N - m)^{-1}$, the lowest nonzero probability allowed by the length of the time series. Thus bias 0 sets the bias toward a cross-ApEn value of 0 in the absence of any matches, whereas bias max sets the bias toward the highest observable value of cross-ApEn.

Cross-ApEn is direction dependent; cross-SampEn is not. Because of the logarithms inside the summation, $\Phi^{m}(r)_{\{v\mid u\}}$ will not generally be equal to $\Phi^{m}(r)_{\{u\mid v\}}$. Thus cross-ApEn($m$, $r$, $N$)($v\mid u$) and its direction conjugate cross-ApEn($m$, $r$, $N$)($u\mid v$) are unequal in most cases.

In defining cross-SampEn, we set $B^{m}(r)_{\{v\mid u\}}$ as $(N - m)^{-1}$ times the number of vectors $y_{m}(j)$ within $r$ of $x_{m}(i)$, where $j$ ranges from 1 to $N - m$. We then defined $A^{m}(r)_{\{v\mid u\}}$ as $(N - m)^{-1}$ $\sum_{u = 1}^{m} A^{m}(r)_{\{v\mid u\}}$. Finally, we set cross-SampEn($m$, $r$, $N$)($v\mid u$) and its direction conjugate cross-SampEn($m$, $r$, $N$)($u\mid v$) to be assigned to a template yielding no matches at all.

Because of the logarithms inside the summation, ApEn and SampEn can be calculated analytically for series of random numbers. ApEn and SampEn derive from formulas suggested to estimate the Kolmogorov entropy of a process represented by a time series. At their root, each is a measurement of the conditional probability that two vectors that are close to each other for $m$ points will remain close at the next point. There are several models, including sets of iid random numbers, for which the theoretical values of the parameters ApEn($m$, $r$) and SampEn($m$, $r$) can be calculated. We show here the case of uniform random numbers, for which the theoretical values of ApEn and SampEn are nearly identical.

The number of pairs that match is clearly independent of which series is the template and which is the target. Because the last summation is equal to $(N - m)^{2}$ $B^{m}(r)_{\{v\mid u\}}$, it follows that $B^{m}(r)_{\{v\mid u\}}$ is also direction independent, implying that cross-SampEn($m$, $r$, $N$)($v\mid u$) = cross-SampEn($m$, $r$, $N$)($u\mid v$). We further noted that cross-SampEn will be defined provided that $A^{m}(r)_{\{v\mid u\}} \neq 0$. Cross-SampEn, on the other hand, requires only that one pair of vectors in the two series match for $m+1$ points.

We calculated cross-SampEn($1$, $r$, $250$) for the same realizations of the $[\text{MIX}(Q)\mid \text{MIX}(P)]$ pairs used above to test cross-ApEn and over the same range of $r$. In contrast to cross-ApEn($1$, $r$, $250$) $[\text{MIX}(P)\mid \text{MIX}(Q)]$ and cross-ApEn($1$, $r$, $250$) $[\text{MIX}(Q)\mid \text{MIX}(P)]$, cross-SampEn($1$, $r$, $250$) $[\text{MIX}(P)\mid \text{MIX}(Q)]$, which is identical to cross-SampEn($1$, $r$, $250$) $[\text{MIX}(Q)\mid \text{MIX}(P)]$, was defined for all 96 pairs over the entire range of $r$ considered.
The expected value of the key probability can be calculated analytically for series of iid numbers based only on their probabilistic distribution. The numbers’ independence implies that the probability that two randomly selected sequences within $r$SD of each other for the first $m$ points will remain within $r$ at their next points is simply the probability that any two points will be within a distance $r$SD of each other. For random numbers with density function $p(x)$ and standard deviation $SD$, the expression for this probability is $\int_{-\infty}^{\infty} p(t) [\int_{-\infty}^{\infty} p(x) dx] dt$. Because the parameter $ApEn(m, r)$ measures the average of the negative logarithm of this probability, it is expected to return a value of $-\int_{-\infty}^{\infty} p(t) \ln [\int_{-\infty}^{\infty} p(x) dx] dt$ (21). $SampEn(m, r)$, on the other hand, measures the logarithm of the conditional probability and is thus expected to return a value of $-\ln [\int_{-\infty}^{\infty} p(t) [\int_{-\infty}^{\infty} p(x) dx] dt]$.

Because these expressions for the expected values of the parameters $ApEn$ and $SampEn$ depend solely on $r$ and the probabilistic character of the data, uniform random numbers provide a benchmark for testing the estimation of $ApEn$ over a range of parameters. In particular, $ApEn$ and $SampEn$ are expected to give identical results for uniformly distributed random numbers. Figure 1A shows a histogram of the random numbers used and an excerpt from the sequence (inset). Taking the derivative of $-\int_{-\infty}^{\infty} p(t) \ln [\int_{-\infty}^{\infty} p(x) dx] dt$ with respect to $\ln (r)$ reveals that, for small $r$ (in this case $r \leq 1$), $ApEn(m, r)$ decreases in proportion to $\ln (r)$ for small $r$. This result generalizes to random numbers with other distributions provided that their density functions are smoothly continuous and bounded. The expected values are shown as the straight line in Fig. 1B. For random numbers with other distributions, the theoretical values of $ApEn$ and $SampEn$ will differ slightly. This is explained by noting that because $-\ln$ is a convex function, Jensen’s inequality (4) applied to each of the integral expressions implies that the $ApEn$ is expected to return a value greater than or equal to $SampEn$.

### RESULTS AND DISCUSSION

$SampEn$ agrees with theory more closely than $ApEn$. For most processes, $ApEn$ statistics are expected to have two properties. First, the conditional probability that sequences within $r$ of each other remain within $r$ should decrease as $r$ decreases and the criterion for matching becomes more stringent. In other words, $ApEn(m, r, N)$ should increase as $r$ decreases (22, 27). This expected property is demonstrated in Fig. 1B by the straight line, which plots the theoretically predicted values of $ApEn$ and $SampEn$. Second, $ApEn$ should be independent of record length. The plot of theoretical values of $ApEn$ and $SampEn$ in Fig. 1B illustrates this expectation. Because of their similarity, we expect $SampEn$ statistics to exhibit similar properties. It has been suggested that record lengths of $10^m-20^m$ should be sufficient to estimate $ApEn(m, r)$ (27).

We tested $ApEn$ and $SampEn$ statistics on uniform, iid random numbers, because the results could be compared with the analytically calculated expected values. Figure 1, B and C, shows the performance of $ApEn(2, r, N)$ and $SampEn(2, r, N)$ on uniform iid random numbers. $SampEn(2, r, N)$ very closely matches the expected results for $r \geq 0.03$ and $N \geq 100$ (Fig. 1, B and C), whereas $ApEn(2, r, N)$ differs markedly from expectations for $N < 1,000$ and $r < 0.2$. Figure 2 shows $SampEn$ and $ApEn$ as functions of $r$ ($m = 2$) for three sets of uniform random numbers consisting of 100, 5,000, and 20,000 points. $SampEn$ statistics for $r = 0.2$ are in agreement with theory for much shorter data sets. We investigated the general applicability of $SampEn$ and $ApEn$ statistics to random numbers with other distributions. The analysis of numbers with Gaussian, exponential, and $\gamma$-distributions with parameter $\lambda = 1, 2, \ldots, 10$ gave results essentially identical to those shown in Fig. 1.
SampEn shows relative consistency where ApEn does not. A critically important expected feature of ApEn is relative consistency (22, 27). That is, it is expected that, for most processes, if \( \text{ApEn}(m_1, r_1)(S) = \text{ApEn}(m_1, r_1)(T) \), then \( \text{ApEn}(m_2, r_2)(S) \leq \text{ApEn}(m_2, r_2)(T) \). That is, if record \( S \) exhibits more regularity than record \( T \) for one pair of parameters \( m_1 \) and \( r_1 \), it is expected to do so for all other pairs. Graphically, plots of ApEn as a function of \( r \) for different data sets should not cross over one another. The determination that one set of data exhibits greater regularity than another can be made only when this condition is met. We tested this expectation using 1,000-point realizations of the MIX(\( p \)) process, where the degree of order could be specified. Figure 3A shows that the ApEn statistics of the less-ordered MIX(\( 0.9 \)) which has, on average, few matches of length \( m \) for a given template (small \( B_i \)) for small \( r \), rises as a function of \( r \) and crosses over a plot of ApEn statistics of the more-ordered MIX(\( 0.1 \)). For \( r < 0.05 \), one would conclude incorrectly that MIX(\( 0.9 \)) was more ordered than MIX(\( 0.1 \)). Thus relative consistency does not hold for ApEn statistics.

We investigated the mechanism responsible for this lack of relative consistency. Note that, for \( r = 0.5 \), ApEn statistics correctly distinguished MIX(\( 0.1 \)) and MIX(\( 0.9 \)). For this value of \( r \), the MIX(\( 0.1 \)) data yielded an average of \( > 46 \) matches per template and \( \approx 28 \) forward matches per template, whereas the MIX(\( 0.9 \)) data yielded \( \approx 37 \) and \( 10 \), respectively. These large numbers of matches render the bias insignificant; that is, the unbiased \( A/B, (28/46 \) and \( 10/37 \) is not very different from the biased \( (A_1 + 1)/(B_1 + 1) \) (29/47 and 11/38). As \( r \) is decreased, however, the number of template matches decreased more for the MIX(\( 0.9 \)) data than for the MIX(\( 0.1 \)) data. This made the bias significant for MIX(\( 0.9 \)) data under conditions for which it was insignificant in the MIX(\( 0.1 \)) data. For example, when \( r = 0.05 \), ApEn(\( 2, r, 1,000 \)) of MIX(\( 0.1 \)) was 0.463, whereas the value for MIX(\( 0.9 \)) was 0.505. The spurious similarity of the ApEn statistics is due to bias. The MIX(\( 0.1 \)) data yielded \( \approx 27 \) matches per template and \( \approx 22 \) forward matches, whereas the MIX(\( 0.9 \)) data yielded only 0.45 and 0.01, respectively. Thus more than one-half of the templates of the MIX(\( 0.9 \)) data matched no other templates and were assigned a conditional probability of 1. In this example, ApEn statistics lack relative consistency, because less-ordered data sets have fewer matching templates and are more vulnerable to the bias generated by self-matches. SampEn analysis of the same data, on the other hand, reports correctly over the whole range of \( r \) (Fig. 3B).

Are SampEn statistics relatively consistent? We have shown that SampEn statistics appear to be relatively consistent over the family of MIX(\( p \)) processes, whereas ApEn statistics are not. Although we believe that relative consistency should be preserved for processes for which probabilistic character is understood, we see no general reason why ApEn or SampEn statistics should remain relatively consistent for all time series and all choices of parameters.

We propose a general, but by no means exhaustive, explanation for this phenomenon. SampEn is, in essence, an event-counting statistic, where the events are instances of vectors being similar to one another. When these events are sparse, the statistics are expected to be unstable, which might lead to a lack of relative consistency. Recall that SampEn(\( m, r, N \)) is less than or equal to \( \ln (B) \), the natural logarithm of the number of template matches. Suppose SampEn(\( m, r, N \)) \( \leq \text{SampEn}(m, r, N)(T) \) and that the number of \( T \)'s template matches, \( B_T \), is less than the number of \( S \)'s template matches, \( B_S \), which would be consistent with \( T \) displaying less order than \( S \). Provided that \( A_T \) and \( A_S \), the number of forward matches, are relatively large, both
SampEn statistics will be considerably lower than their upper bounds. As $r$ decreases, $B_1$ and $A_1$ are expected to decrease more rapidly than $B_T$ and $A_S$. Thus, as $B_T$ becomes very small, SampEn($m, r, N$) will begin to decrease, approaching the value $\ln(B_1)$, and could cross over a graph of SampEn($m, r, N$)($S$), where or while $B_T$ is still relatively large. Furthermore, as the number of template matches decreases, small changes in the number of forward matches can have a large effect on the observed conditional probability. Thus the discrete nature of the SampEn probability estimation could lead to small degrees of crossover and intermittent failure of relative consistency, and we cannot say that SampEn will always be relatively consistent. We have shown, however, that SampEn is relatively consistent for conditions where ApEn is not, and we have not observed any circumstance where ApEn maintains relative consistency and SampEn does not.

One source of the residual bias in SampEn is correlation of templates. Although more consonant with theory than ApEn, we found that SampEn statistics deviated from predictions for very short data sets. For $10^5$ sets of Gaussian random numbers with $m = 2$, and $r = 0.2$, we found that the deviation was $<3\%$ for record lengths $>100$ but as high as $35\%$ for sets of 15 points. Figure 3C shows the biased results of SampEn($2, 0.2, N$) for the range of $4 \leq N \leq 100$. We suspected that the integral expressions for the parameters ApEn($m, r$) and SampEn($m, r$) could not be used as expected values of the statistics ApEn($m, r, N$) and SampEn($m, r, N$) under all conditions, because the expressions relied on the assumption that the templates were independent of one another. As $N$ decreases and $m$ increases, however, a larger proportion of templates are comprised of overlapping segments of the record and are thus not independent. Because of this correlation, results might deviate from predictions for short data sets. We thus tested the hypothesis that the majority of the bias results from nonindependence of the templates.

One way to test the hypothesis is to compare observed values of SampEn with those obtained from a model accounting for template correlation. The hypothesis predicts that the values should match. We tested the simplest case of $m = 2$ and $N = 4$, where a data set can be represented by $(w, x, y, z)$, so that there are exactly two vectors of length $m = 3$, $(w, x, y)$ and $(x, y, z)$. If $(w, x)$ is close to $(x, y)$, it stands to reason that $(w, x, y)$ will have a higher than expected probability of being close to $(x, y, z)$. Formally, the conditional probability that $(w, x)$ and $(x, y)$ are close is $[\text{corr}(w, x) \text{corr}(w, y)]/[\text{corr}(x, y) \text{corr}(y, z)]$, where $\text{corr}(w, x)$ is the Gaussian density function.

A second way to test the hypothesis is to calculate SampEn statistics for one set of data under two conditions: with and without overlapping templates. The hypothesis predicts that the results should not match. For this test, we chose the case of $m = 2$ and $N = 6$, the shortest record containing two nonoverlapping templates of length $m + 1 = 3$. We can represent each set as $(a, b, c, x, y, z)$. For $10^6$ sets of six Gaussian random numbers, we calculated the conditional probability that $(a, b, c)$ was within $r$ of $(x, y, z)$ given that their first two points were close, thus calculating the probability for pairs of disjoint templates. The result was 0.111, very close to the expected 0.112 for independent templates. For the same number sets, we then calculated the average value of SampEn$(2, 0.2, 6)$, and the result was 0.094. Thus the two results do not match, in support of the hypothesis. We conclude from this analysis that the statistics SampEn($m, r, N$) are not completely unbiased under all conditions and that the bias of SampEn for very small data sets is largely due to nonindependence of templates.

One method for removing this bias would be to partition the time series $[u_i | 1 \leq i \leq N]$ into the $m + 1$ sets of neighboring, disjoint vectors of length $m + 1$ $X_i = ([u_i, u_{i+k+1}], [u_{i+k}, u_{i+k+1}], \ldots, [u_{i+k}, u_{i+k+1}])$, where $i = (N - (m + 1))/(m + 1)$, so that there are $N - (m + 1)$ intervals, each containing $m + 1$ elements. Because this bias appears to be present only for very small $N$, the disjoint template approach does not appear necessary in usual practice.

Cross-SampEn shows relative consistency where cross-ApEn does not. As noted above, an essential feature of the measures of order is their relative consistency. That is, if one series is more ordered than another, it should have lower values of ApEn and SampEn for all conditions. We can extend this idea to cross-ApEn and cross-SampEn; if a pair of series is more synchronous than another pair, it should have lower values of cross-ApEn and cross-SampEn statistics for all conditions tested.

We tested the ability of cross-ApEn and cross-SampEn to distinguish between MIX(0.1) and the less-ordered MIX(0.6) processes. The strategy was to compare each with the intermediate MIX(0.3) process. The expected result was that the [MIX(0.3), MIX(0.1)] pairs should appear more ordered than the [MIX(0.3), MIX(0.6)] pair, because MIX(0.1) is significantly more ordered than MIX(0.6). That is, cross-ApEn($2, r, 250$) [MIX(0.3)||MIX(0.1)] should be less than cross-ApEn($2, r, 250$) [MIX(0.3)||MIX(0.6)], and cross-
SampEn(2, r, 250) \([\text{MIX}(0.3) \| \text{MIX}(0.1)]\) should be less than cross-SampEn(2, r, 250) \([\text{MIX}(0.3) \| \text{MIX}(0.6)]\).

We tested this prediction bidirectionally, that is, \(\text{MIX}(0.3)\) served as the template series for one analysis and as the target series for the next, and over a range of tolerances \(r\) by using the bias-max and bias-0 strategies for ensuring that cross-ApEn was defined. The results are shown in Fig. 4. \(\text{MIX}(0.3)\) was the template series in Fig. 4, \(C\) and \(E\), and the target series in Fig. 4, \(D\) and \(F\).

The expected result is that cross-ApEn and cross-SampEn should be less for the \([\text{MIX}(0.3) \| \text{MIX}(0.1)]\) pair than for the \([\text{MIX}(0.3) \| \text{MIX}(0.6)]\) pair. That is, the circles should always be below the squares. We found this to be true for only one of the four tests of cross-ApEn, the case of using \(\text{MIX}(0.3)\) as the target series with the bias-max correction strategy (Fig. 4D). In the other cases, the order of results was reversed (Fig. 4C) or crossed over (Fig. 4E and F). As shown in Fig. 4B, cross-SampEn returned the expected results with a high degree of confidence across the range of tolerances \(r\).

Thus cross-ApEn statistics fail as a means of judging the relative order of two time series by their similarity to a third series. In practice, however, cross-ApEn has been used differently: to determine the relative synchrony of two pairs of time series of clinical data from different patients. We thus tested cross-ApEn and cross-SampEn on two sections of a long multivariate cardiovascular time series used in the 1991 Santa Fe competition for time series forecasting (35). The series consisted of concurrent measurements of a sleeping patient’s heart rate (hr) and chest volume (cv).

Fig. 5. Cross-ApEn results can vary greatly because of direction effects and correction strategy employed. Shown are calculations of cross-ApEn statistics of two 250-point segments of multivariate clinical cardiovascular time series used in 1991 Santa Fe time-series forecasting competition. Cross-ApEn was calculated for concurrent series of heart rate (hr) and chest volume (cv). A: Key to time series and direction of analysis (same conventions as Fig. 4A). B: cross-ApEn(1, r, 250)(cv\|hr) of 2 pairs of series. C: cross-ApEn(1, r, 250)(cv\|hr) for 2 segments of series with bias-max correction. D: same as C, but with direction of analysis reversed to show cross-ApEn(1, r, 250)(hr\|cv), rather than cross-ApEn(1, r, 250)(hr\|cv). E: identical to C, but with bias-0, rather than bias-max, correction. F: identical to D, but with bias-0, rather than bias-max, correction.

Cross-SampEn distinguishes these clinical data in a consistent fashion.
compared the pairs (hr1,cv1) and (hr2,cv2) shown in Fig. 5A, excerpted from the larger time series. Here, the expected result was not known beforehand, and our question was whether one pair consistently appeared more synchronous than the other. This is an extension of the expected relative consistency of ApEn discussed above.

Figure 5 shows the results for N = 250, m = 1, and a range of r. We set m = 1, in accordance with published practice for analyzing series of similar length (28), and the record length of N = 250 exceeds the 10m−2m points recommended for ApEn analysis (27). Time series are shown in Fig. 5A. The question is whether the pair (hr1,cv1) has more joint synchrony than the pair (hr2,cv2). The expected result is that the circles should be consistently higher or lower than the squares for Fig. 5, D–F. This was not the case; conclusions about relative synchrony by use of cross-ApEn analysis depended on which series served as the template and on the correction strategy, and there was no consistent result. Cross-SampEn, on the other hand, consistently reported that (hr1,cv1) had more joint synchrony than (hr2,cv2) (Fig. 5B).

For 32 sets of these data, we further examined the correction methods, calculating cross-ApEn(m, r, N) (cv)/hr and cross-ApEn(m, r, N) (hr)/cv for each set. For the relaxed condition of r = 1.0, we found that cross-ApEn(1,1,250)(cv)/hr was defined for only 19 of the 32 cases, whereas cross-ApEn(1,1,250)(hr)/cv was defined for only 12 cases. For the more stringent case of r = 0.2, cross-ApEn(1,0.2,250)(cv)/hr was never defined, whereas cross-ApEn(1,0.2,250) (hr)/cv was defined for 2 of the 32 cases. By contrast, for all r ≥ 0.08, cross-SampEn(1,r,250)(cv)/hr was defined for each of the 32 pairs. Thus cross-SampEn had a more consistent performance for evaluating these clinical cardiovascular data.

Summary. We have developed and characterized SampEn, a new family of statistics measuring complexity and regularity of clinical and experimental time series data and compared it with ApEn, a similar family. We find that SampEn statistics 1) agree much better than ApEn statistics with theory for random numbers with known probabilistic character over a broad range of operating conditions, 2) maintain relative consistency where ApEn statistics do not, and 3) have residual bias for very short record lengths, in a large part because of nonindependence of templates. Furthermore, cross-SampEn is a more consistent measure of joint synchrony of pairs of clinical cardiovascular time series. We attribute the difficulties of ApEn analysis to the practice of counting self-matches and of cross-ApEn to the problem of unmatched templates resulting in undefined probabilities. The differences are that SampEn does not count templates as matching themselves and does not employ a template-wise strategy for calculating probabilities. SampEn statistics provide an improved evaluation of time series regularity and should be a useful tool in studies of the dynamics of human cardiovascular physiology.

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