Herzschr Elektrophys 11:139–150 (2000)

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Approximate entropy in cardiology

Received: 30 March 2000
Accepted: 1 May 2000

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Summary *Background*. The quantification of subtle patterns in sequential data, and their changes, has considerable potential utility throughout cardiology, including the analysis of heart rate rhythms. *Aim of the study.* Approximate entropy (ApEn), a recently developed statistic quantifying serial irregularity, has been applied in numerous studies throughout mathematics and applications, especially biology. We indicate results to date, and future direction, of interest to cardiologists. *Methods.* We define ApEn, indicating basic properties. We discuss typical applications of ApEn, with special focus on a representative aspect of ApEn applications to heart rate dynamics, to pre- and early life studies. Subsequently, we introduce and briefly discuss cross-ApEn, a thematically similar quantification of two-variable asynchrony. *Results.* ApEn consistently detects subtle shifts in heart rate rhythmicity in many studies in which mean levels and classical variability assessments fail to discriminate normative from pathophysiological subjects. Greater regularity (lower ApEn) clinically corresponds to compromised physiology in all cardiologic settings discussed herein. We provide a mechanistic interpretation of lowered ApEn values, based on mathematical analysis, yet linked to physiology. We discuss and clarify why ApEn is complementary to classical 'moment analysis', to chaos-related statistical measures, and to spectral and correlation measures, and oftentimes provides clearer discriminatory capability. *Conclusions.* Both ApEn and cross-ApEn have significant potential to consequentially enhance present statistical methodologies of analysis of cardiologic data, in both clinical and in research settings.

Key words Approximate entropy – irregularity – asynchrony – complexity – variability – heart rate

Introduction

Series of sequential data arise throughout medicine, in a myriad of contexts. Within cardiology, two essential examples are heart rate (often R-R interval) and ECG time-series; related respiratory time-series are often also of interest in many instances. Enhanced capabilities to quantify differences among such series would be extremely valuable, since these series reflect primary physiological information. Although practitioners and researchers typically quantify mean levels, or rates, and oftentimes the extent of variability, it is recognized that in many instances, the persistence of certain patterns, or shifts in an 'apparent ensemble amount of randomness', provide the fundamental insight of subject status. Despite this recognition, formulas and algorithms to quantify an 'extent of randomness' have not been developed and/or utilized in the above contexts, primarily since even within mathematics itself, such a quantification technology was lacking until very recently.

Thus except for the settings in which egregious (changes in) serial features presented themselves, which specialists are trained to visually detect, subtler changes in patterns would largely remain undetected, unquantified, and/or not acted upon.

Recently, a new mathematical approach and formula, approximate entropy (ApEn), has been introduced as a quantification of *regularity* of data, motivated by both the above application needs (29), and by fundamental questions within mathematics (38, 42). This approach calibrates an ensemble extent of sequential interrelationships, quantifying a continuum that ranges from totally ordered to completely random. The central focus of this article is to discuss ApEn, and its application to cardiology time-series, especially the heart rate series, to indicate both results to date and potential further applications.

Before presenting a discussion of regularity, we consider an example (Fig. 1) to illustrate what we are trying to measure. In Fig. 1, the data represent the beat-to-beat heart rate, in beats per minute, at equally spaced time intervals. *Tracing* (A) is from an infant who had an aborted SIDS (Sudden Infant Death Syndrome) episode 1 week prior to the recording, and (B) is from a healthy infant (33). The standard deviations (SD) of these two tracings are approximately equal, and while the aborted SIDS infant has a somewhat higher mean heart rate, both are well within the normal range. Yet tracing (A) appears to be more regular than tracing (B). We ask (i) how do we quantify the apparent differences in regularity?; (ii) do the regularity values significantly distinguish the data sets?; (iii) how do inherent limitations posed by moderate length time-series, with noise and measurement inaccuracy present, affect statistical analyses?; (iv) is there some general mechanistic hypothesis, applicable to diverse contexts, that might explain such regularity differences?

Historical context further frames this effort. Several complexity measures, e.g., K-S entropy, Lyapunov spectra, correlation dimension (16, 17, 20), have been developed for and are properly employed on truly chaotic processes. Chaos refers to output from deterministic dynamical systems, where the output is bounded and aperiodic, thus appearing partially "random". Recently, there have been myriad claims of chaos based on analysis of experimental time-series data, in which correlation between successive measurements has been observed. Since chaotic systems represent only one of many paradigms that can produce serial correlation, it is generally inappropriate to infer chaos from the correlation alone. The mislabeling of correlated data as "chaotic" is a relatively benign offense. Of greater significance, complexity statistics that were developed for application to chaotic systems and are relatively limited in scope have been commonly misapplied to finite, noisy and/or stochastically derived time-series, frequently with confounding and non-replicable results. This caveat is particularly germane to biologic signals, especially those taken in vivo, as such signals usually represent the output of a complicated network with both stochastic and deterministic components. We elaborate on these points below. With the development of ApEn, we can now successfully handle the noise, data length, and stochastic/composite model constraints in statistical applications.

We also briefly discuss cross-ApEn (40, 42), a quantification of asynchrony or conditional irregularity between two signals. Cross-ApEn is thematically and algorithmically quite similar to ApEn, yet with a critical difference in focus: it is applied to two time-series, rather than a single series, and thus affords a distinct tool from which changes in the extent of synchrony in interconnected *systems* or *networks* can be directly determined. This quantification strategy is thus especially germane to many biological feedback and/or control systems and models for which cross-correlation and cross-spectral methods fail to

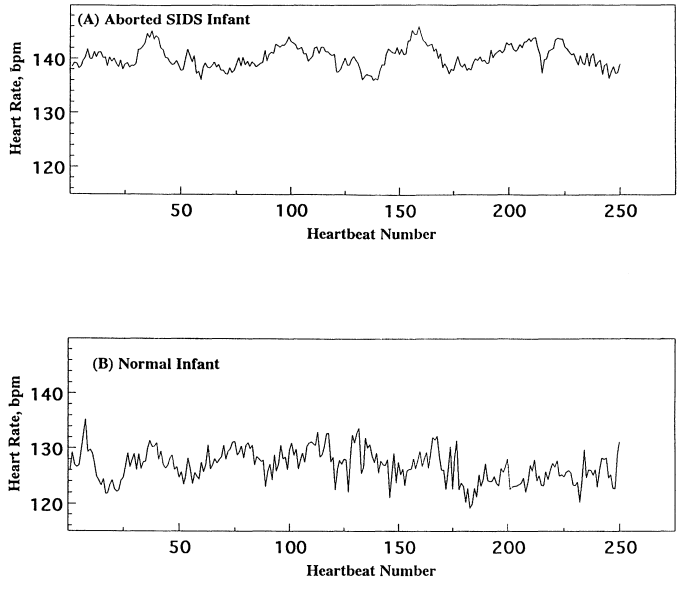

Fig. 1 Comparison of quiet sleep heart rate tracings with similar variability, VAR. **A** Tracing from aborted SIDS infant, VAR = 17.9 ms, ApEn = 0.742; **B** Tracing from normal infant, VAR = 17.2 ms, ApEn = 1.457

fully highlight markedly changing features of the data sets under consideration. To date, this has been applied in numerous endocrinologic applications. We believe that potential applications within cardiology are significant, especially to heart rate–respiratory paired time-series, and possibly to paired heart rate–EEG series, as well.

The organization of the rest of this article is as follows. First, we define ApEn, and indicate some basic properties. Then a relatively brief overview of some representative applications of ApEn to both biology and cardiology is given. Next, we provide somewhat greater depth on one aspect of ApEn applications to heart rate dynamics, to pre- and early life studies. We then indicate a mechanistic explanation between lowered ApEn values and compromised physiology. Subsequently, we discuss cross-ApEn, indicated above. We next give a bit more mathematical discussion on the relationship between ApEn and other statistical approaches to time-series analysis, to both 'chaos-related' measures, and to spectral and correlation measures. Finally, we conclude and suggest several areas for new applications of ApEn (and cross-ApEn).

Quantification of regularity, ApEn

To quantify irregularity, we utilize approximate entropy, ApEn, a model-independent statistic defined in ref. (29), with further mathematical properties and representative biological applications given in refs. (14, 34, 38, 41–44). Approximate entropy (ApEn), was introduced as a quantification of regularity in sequences and time-series data, initially motivated by applications to relatively short, noisy data sets (29). Mathematically, ApEn is part of a general development of approximating Markov Chains to a process (30); it is furthermore employed to refine the formulations of independent, identically distributed random variables, and normal numbers in number theory, via rates of convergence of a deficit from maximal irregularity (38, 42, 43). Analytical properties for ApEn can be found in refs. (29, 36, 37, 42); as well, it provides a finite sequence formulation of randomness, via proximity to maximal irregularity (38, 42). Statistical evaluation is given in refs. (36 and 37).

ApEn assigns a nonnegative number to a sequence or time-series, with larger values corresponding to greater apparent process randomness or serial irregularity, and smaller values corresponding to more instances of recognizable features or patterns in the data. Two input parameters, a run length *m* and a tolerance window *r*, must be specified to compute ApEn. Briefly, ApEn measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on the next incremental comparison. The opposing extremes are perfectly regular sequences, (e.g., sinusoidal behavior, very low ApEn), and independent sequential processes (very large ApEn). It is imperative to consider ApEn(m,r) as a *family* of parameters; comparisons are intended with fixed m and r.

Formally, given N data points u(1), u(2),… u(N), two input parameters, m and r, must be fixed to compute ApEn (denoted precisely by ApEn(m,r,N)). To define ApEn, first form vector-sequences x(1) through x(N–m+1) from the {u(i)}, defined by x(i)=[u(i),…, u(i+m–1)]. These vectors represent m consecutive u-values, commencing with the i^{th} point. Define the distance d[x(i),x(j)] between vectors x(i) and x(j) as the maximum difference in their respective scalar components. Use the sequence x(1), x(2),… x(N–m+1) to construct, for each $i \leq N-m+1$, $C_i^m(r)$=(number of x(j) such that $d[x(i),x(j)] \leq r)/(N-m+1)$. The $C_i^m(r)$'s measure *within a tolerance r* the regularity, or frequency, of patterns similar to a given pattern *of window length m*. Next, define $\Phi^m(r)$ as the average value of $\ln C_i^m(r)$, where ln is the natural logarithm. We define approximate entropy by $ApEn(m,r,N) = \Phi^m(r) - \Phi^{m+1}(r)$.

ApEn evaluates both dominant and subordinant patterns in data; notably, it will detect changes in underlying episodic behavior not reflected in peak occurrences or amplitudes (39). Additionally, ApEn provides a direct barometer of feedback system change in many coupled systems (31, 39).

For the studies discussed herein, ApEn values for all data sets were calculated with widely established parameter values of m=1 or m=2, and with r a fixed value between 0.1 to 0.25 SD of the standard deviation (SD) of the individual subject time-series. *Normalizing* r to each time-series SD in this manner gives ApEn translation- and scale-invariance (33), in that it remains unchanged under uniform process magnification, reduction, or constant shift higher or lower. Multiple previous studies that included both theoretical analysis (29, 36, 39) and clinical applications (18, 33–35, 40, 41, 45, 56) have demonstrated that these input parameters produce good statistical reproducibility for ApEn for time series of lengths $N \geqslant 60$, as considered herein.

ApEn is typically calculated by a short computer program, with a FORTRAN listing for a "basic" code reference found in ref. ((35), Appendix B). ApEn is nearly unaffected by noise of magnitude below 'r', a *de facto* filter level. ApEn is robust or insensitive to artifacts or outliers: extremely large and small artifacts have a small affects on the ApEn calculation, if they occur infrequently. Both these points are evidently useful in clinical and experimental contexts.

We reinforce a fundamental difference between regularity statistics,

such as ApEn, and variability measures: for variability measures, the order of the input data is irrelevant – the focus is to quantify the degree of spread about a central value. In contrast, for ApEn, discerning changes in order from apparently random to very regular is the primary statistical focus.

Finally, further technical discussion of mathematical and statistical properties of ApEn, including mesh interplay, relative consistency of (m,r) pair choices, asymptotic normality under general assumptions, and error estimation for general processes can be found elsewhere (36, 37). To develop a more intuitive, physiological understanding of the ApEn definition, a multistep description of its typical algorithmic implementation, with figures, is developed in ref. (36).

Representative biological and cardiologic applications

ApEn has been applied to numerous settings both within and outside biology. Within biology and medicine, it has been applied to studies discriminating, e.g., atypical DNA sequences (8), electroencephelograms [EEGs] (4, 46), neuromuscular control (24), and respiratory patterns (10) from normative counterparts. Within endocrinology, it has been employed in multifaceted ways to determine subtle disruptions in pathophysiological or aging hormonal secretory patterns, for many hormones, including insulin (50), growth hormone (34), LH (44), FSH (41), and cortisol (47).

In heart rate studies, ApEn has shown very significant differences in a variety of settings in which moment (mean, SD) statistics did not show clear distinctions. Possibly paramount among goals for new statistical analyses of heart rate data would be prediction techniques for ventricular and for atrial fibrillation (AF), and tachycardia. Recently, ApEn has been shown to be predictive of atrial fibrillation, progressively decreasing from 120 min prior to events until the episode itself (57). Furthermore, ApEn has been shown to quantify subtle differences between ventricular fibrillation (VF) and sinus rhythm (51). Although future studies will be required to specify the contexts in which ApEn may provide the sharpest utility to either or both of VF or AF, the potential utility of such studies, given these initial findings, is considerable.

Additionally, the following representative heart rate applications illustrate the diversity of the applications, both present and potential, for approximate entropy. ApEn has been utilized to show evidence of phase transitions between sleeping and waking states (1). ApEn decreases more in hypertensive patients, and for longer timeframes, than for normotensive patients, suggesting that for hypertensive patients, persistent autonomic activity under the condition of suppressed cardiac complexity may contribute to the unstable hemodynamic insults from the outset of general anesthesia (19). ApEn was seen to predict autonomic dysfunction, and outcome, in patients awaiting liver transplantation (13). In a (conscious) dog study, when hypotension was induced after sympathetic inhibition, ApEn increased, compared to hypotension alone (27). Notably, and conversely, parasympathetic inhibition with hypotension resulted in driving ApEn to nearly 0 (i.e., achieving very regular dynamics). We thus infer that ApEn reflects parasympathetic modulation of heart rate. Finally, ApEn established a gender difference in heart rate dynamics, especially in elderly subjects, with the heart rate patterns of women significantly more irregular than those of matched male subjects (48).

We now provide some more detail on one aspect of ApEn applications to cardiologic and heart rate dynamics, specifically to the setting of pre- and early life. The intent of this focus is twofold: (i) to illustrate several representative findings in a bit of depth, to clarify both scientific and clinical utility of ApEn; (ii) to indicate a continuum interpretation among antepartum, perinatal, and postnatal heart rate analyses. This second point is both important on its own, as well as indicating that results from new quantitative tools can then be synthesized to achieve broader mechanistic application than had previously been considered.

Sample applications: pre- and early life monitoring studies

The utility of fetal heart rate (FHR) analysis, and more broadly, of fetal monitoring itself, has been the subject of much recent controversy. However, it appears that much more use could be made of the FHR data than is currently practiced, with considerable anticipated gain along two distinct directions. First, a considerable amount of pattern-related information in the FHR, above and separate from variability measures, could be of crucial clinical value, yet is currently not assessed and remains clinically ignored. Quantifying and detecting subtle shifts in FHR irregularity (manifesting insidious patterns of physiologic consequence) could well provide important determinants of whether and when to either induce labor or to perform a Caesarean section; such findings would generally be indetectable by auscultation. Secondly, the exclusive focus of present FHR analysis is to determine pre- and intralabor management; inferences and linkages from FHR data towards the potential identification of the high-risk infant are generally not investigated. Based on several studies discussed below, all of which associate more regular (patterned, lower ApEn) heart rate

tracings with compromised physiology, outcome, and inadequate or incomplete network development, we suggest that FHR analyses could be justifiably used as a predictor of postnatal life course.

Fetal monitoring study

Since the inception of fetal monitoring, there has been extensive analysis of variability measures in FHR recordings, to assess fetal well-being. Such analysis distinguishes a "flat" from a "reactive" tracing, but cannot distinguish data as abnormal based on a tendency towards regularity (i.e., low ApEn values) such as seen in sinusoidal heart rates. Broadly, the obstetrician has been trained to recognize a variety of tracings in FHR data as cause for concern: bradycardia and tachycardia, variable and late decelerations, and sinusoidal heart rates. In general, a recognition of particular heart rate patterns indicates to the trained observer that fetal distress may be present. ApEn quantifies such regularity in a manner consistent with intuition; it also quantifies subtler changes in regularity of data that may not be so perceptible to the observer. It is this latter property that holds a promise for new utility in FHR analyses. Motivated by the above perspective, a fetal monitoring study, applied to FHR data, was performed (45), and confirmed the following major hypotheses: (i) ApEn is smaller in truly distressed (acidotic) fetuses than in healthy fetuses ($P < 0.00003$); (ii) ApEn values for non-acidotic fetuses with presumed fetal distress are similar to those from normals. Acidotic fetuses had many more instances (28%) of ApEn hourly values less than 0.8 than did the normal and nonacidotic, presumed distressed fetuses combined (5%), quantitatively reinforcing the association between true distress and a reasonable frequency of highly regular tracings. In contrast, neither the mean FHR nor variability measures significantly distinguished the acidotic fetuses from either the healthy fetuses or the non-acidotic, presumably distressed fetuses. Of particular note, in several "truly distressed labors", other than low hourly ApEn values, there were no noted clinical indications of fetal distress prior to an emergency section. Significant hourly deviations in ApEn generally corresponded to a drug administration (e.g., cocaine, Nubain) or to physiologic changes such as cord compression and its relief.

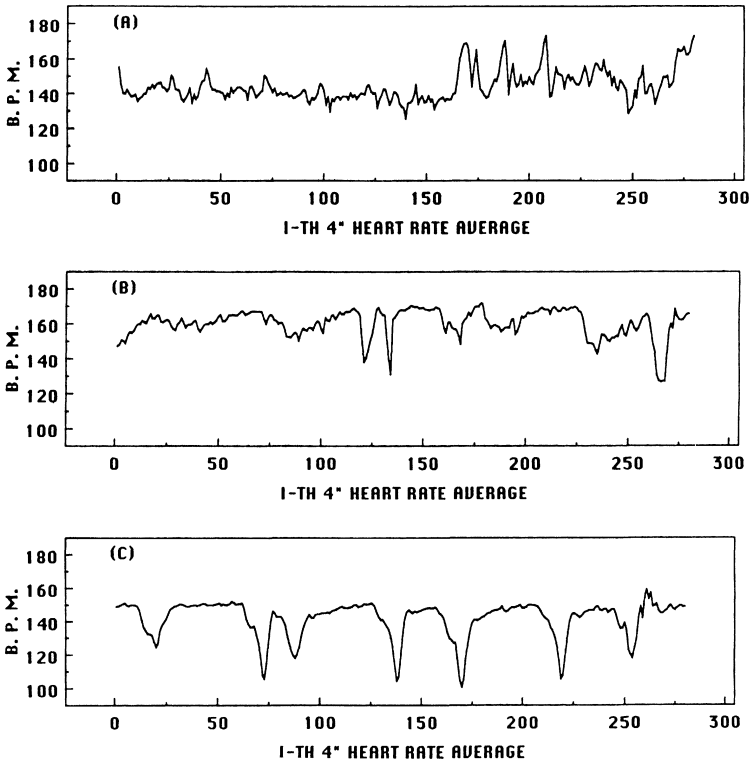

Fig. 2 Comparison of heart rate tracings with similar variability (VAR). Ordinate is beats per minute (B.P.M.), abscissa is time. **A** Tracing from normal fetus, first recorded hour, VAR = 8.10, ApEn = 1.227; **B** Tracing from labor of acidotic fetus, first recorded hour, VAR = 9.06, ApEn = 0.787; **C** Tracing from same fetus shown in (**B**), 1 hour prior to delivery, VAR = 10.34, ApEn = 0.542

Fig. 2 provides greater understanding of the differences in FHR data, quantified by ApEn, that might suggest fetal distress. Tracing (A) corresponds to a normal fetus early in labor, tracing (B) corresponds to an acidotic fetus at a similar early juncture in labor, and tracing (C) corresponds to the same fetus as in (B), 1 hour before delivery. The three tracings, taken from fetal heart rate data in this study, have a similar amount of near-term variability. Tracing (B) has a significantly smaller value of ApEn than tracing (A), and so has greater regularity, though the declaration of clear distress based on recognizable patterns in (B) is hardly apparent. In tracing (C), we see the evolution to regular episodes of bradycardic dips, foreshadowed by the low ApEn value in (B). While traditional means of data analysis and risk assessment might indicate tracing (C) to be from a potentially distressed fetus, such analysis and assessment do not yield the same conclusions from tracing (B). This suggests the use of ApEn in screening for fetal distress, prior to an indication of distress given by more traditional methods.

Moreover, in a significant animal model study of fetal distress, Chaffin et. al. (6) showed a highly pro-

nounced decrease in ApEn in the hypoxic ovine fetus, with the extent of ApEn reduction directly related to the extent of the hypoxia.

Fetal development study

Given the increase in system integration observed in fetal development from 20 weeks gestational age onwards (28), e.g., increased cardiosomatic coupling (53) and increased myelination of the vagus nerve (49), one would hypothesize from the mechanistic interpretation above that ApEn would also generally increase during this period. To study this, fetal heart rate was collected in 14 males and 17 females for 15 min of undisturbed recording using a fetal actocardiograph in conjunction with a Doppler transducer, at 4 week intervals from 20 to 36 weeks gestation (12). During that period, ApEn significantly increased with gestational age. Variability (standard deviation) also increased during this timeframe, but in a complementary and noncoincident manner to that for ApEn, in that a gender difference was seen between male and female ApEn evolution, whereas no gender distinctions were correlated to variability evolution. The ApEn difference in gender-based developments is physiologically interesting, since the manner and timeframe of the gender difference parallels that of fetal lung maturation (23, 26, 58), suggesting ApEn as a specific correlate of cardiorespiratory development. This clinically correlates with the observation that preterm females have superior survival rates compared to corresponding males, especially among the very premature.

Notably, as well, the increase of ApEn with gestational age was confirmed by analysis of 80 fetal magnetocardiograms (FMCGs) in 19 healthy fetuses between the 16th and 41st week of gestation (55). Indeed, for reasons discussed in ref. (55), FMCGs may be a preferred means of obtaining reasonably accurate fetal heart rates. In any case, the qualitatively similar results achieved via distinct data collection techniques reinforce the primary finding.

Early life heart rate analysis

A study of healthy newborn piglets up to 33 days of age showed significantly increasing heart rate irregularity with autonomic maturation, and furthermore, an apparent attenuation of heartbeat irregularity when right stellate ganglion innervation is interrupted (21). This provides empirical physiologic support postnatally of the mechanistic hypothesis (below) associating ApEn as a statistical marker of network development and, concomitantly, that lower ApEn values mark decreased resilience of an organism to adapt to stressful inputs. In a study of heart rate data from normal and aborted Sudden Infant Death Syndrome (SIDS) infants (33), 50% of aborted SIDS infants showed greater ApEn instability across quiet sleep than any normal infant exhibited. This suggests that autonomic regulation of heart rate *occasionally* becomes abnormal in a high-risk subject. Of note, there was a clear association between abnormally low ApEn values and aborted SIDS events: 5 of 14 aborted SIDS infants had at least one quiet sleep epoch with at least 1 ApEn value below the minimum of 45 normal infant ApEn values. Nevertheless, much of the time in aborted SIDS infants, and virtually all the time in healthy infants, the heart rate exhibits a standard amount of irregularity. Thus, we infer a probabilistic phenomenon: the near-miss (and possibly SIDS) infant has a fundamentally unstable autonomic nervous system, manifested by occasional dangerous regimes, in which the heart rate is significantly more regulated than otherwise. As well, this determination that occasional instabilities mark high risk is a fundamentally different perspective than that which is generally held, of consistent, insidious behavior, which furthermore indicates that *signal averaging* distinct epochs may blur, rather than highlight, the detection of settings with insidious pathophysiology.

Fig. 1, referred to in the Introduction, provides further understanding of the quantification of an irregular difference (here, between normal and aborted SIDS infants). The RR interval time-series from the normal and aborted SIDS infant have comparable overall variability, 'VAR', as indicated in the legend. ApEn quantifies the difference in apparent regularity between these data: ApEn = 0.742 for (A), and ApEn = 1.457 for (B). ApEn is thus seen to describe the greater regularity given by the several instances of "apparent, approximately periodic" segments seen in the aborted SIDS infant heart rates.

In another study comparing groups of asphyxiated neonates (severe respiratory distress, persistent pulmonary hypertension, heart failure) to healthy neonates (35), matched for primary clinical variables, the unhealthy neonates exhibited significantly lower ApEn values than the healthy group. A serial study was also performed on a septic infant with persistent pulmonary hypertension (birth weight, 1090 g; gestational age, 27 weeks), with a large and steady increase in ApEn coincident with recovery of the infant (35).

Synthesis

The pre- and early-life studies, taken in ensemble, in conjunction with the mechanistic interpretation below, suggest associations between low (heart rate) ApEn values in-utero and compromised development in the neonate and young infant, indicating possible autonomic nervous system dysfunction, which future

longitudinal studies should clarify. More broadly, these findings suggest a continuum interpretation among antepartum, perinatal, and postnatal heart rate analyses. This perspective is in counterpoint to that *de facto* employed by practitioners, wherein the pre-, peri- and post-natal states are generally considered as discrete, separate epochs, whose findings are applied to more locally time-limited diagnoses. In particular, we postulate that persistence of atypically low heart rate irregularity along an extended timeframe, either pre- and postnatally, or exclusively postnatally, may become an important early marker for long-term autonomic dysfunction and/or significantly increased risk for SIDS.

Mechanistic interpretation for altered regularity

It seems important to determine a unifying theme suggesting greater signal regularity in a diverse range of complicated cardiologic settings. We would hardly expect a single mathematical model, or even a single family of models, to govern a wide range of contexts; furthermore, we would expect that *in vivo,* each heart rate (R-R) or ECG signal would usually represent the output of a complex, multinodal network with both stochastic and deterministic components. Our mechanistic hypothesis is that in a variety of systems, greater regularity (lower ApEn) corresponds to greater component and subsystem autonomy. This hypothesis has been mathematically established via analysis of several very different, representational (stochastic and deterministic) mathematical model forms, conferring a robustness to model form of the hypothesis (31, 39). Restated contrapuntally, ApEn typically increases with greater system coupling and feedback, and greater external influences, thus providing an explicit barometer of autonomy in many coupled, complicated systems.

A proposed mechanistic hypothesis, consistent with all heart rate findings discussed herein, is that, in a variety of composite systems, greater regularity (lower ApEn) corresponds to greater component and subsystem isolation, and clinically correlates with compromised physiology. The point is that in many contexts, apparently including heart rate and EEG settings, 'healthy', more developed systems have good lines of communication, which reflect the integration of both the numbers of external influences that interact and the extent of this interaction. In such settings, pathology represents incomplete system development and/or lessening external inputs, in effect isolating a central system component and critical nodes from their ambient universe. Crucial biological messages are either slow to transmit and receive, or unable to arrive. From an output signal perspective, the base system contributes a more dominant component of the observed time series, manifested in more regular (lower ApEn) output.

Empirically, increasing ApEn in the early life studies (12, 21, 33, 35, 55) and decreasing ApEn with advancing age (18 and 48) suggest that network development early and conversely network decay later in life are calibrated by ApEn. Furthermore, this perspective suggests that since cardiovascular network development and myelination are ongoing processes during fetal development and early life, (quantitative) assessments of such development made at earlier stages could provide clinically relevant predictive information of subsequent developments.

Cross-ApEn

Cross-ApEn is a measure of asynchrony between two time-series (40, 42); representative applications are given in refs. (40, 47, 56). Similarly to ApEn, it is a two parameter family of statistics, with m and r taking the same meaning as in the ApEn setting, herein fixed for application to the paired time-series {u(i)},{v(i)}. Cross-ApEn measures, within tolerance *r,* the (conditional) regularity or frequency of v-patterns similar to a given u-pattern of window length *m.* It is typically applied to *standardized* u and v time-series. Greater asynchrony indicates fewer instances of (sub)pattern matches, quantified by larger cross-ApEn values. Fig. 3, taken from a recent study of paired ACTH-cortisol endocrine hormonal secretory dynamics in Cushing's disease (47), illustrates the cross-ApEn quantification, with greater ACTH-cortisol secretory asynchrony in the diseased subject, compared to the control.

Cross-ApEn is generally applied to compare sequences from two distinct yet intertwined variables in a network. Thus we can directly assess network, and not just nodal, evolution, under different settings – e.g., to evaluate uncoupling, and/or changes in feedback and control. Hence, cross-ApEn facilitates analyses of output from myriad complicated networks, avoiding the requirement to model the underlying system. This is especially important, since accurate modeling of (physiological) networks is often nearly impossible – even full description of all system nodes and pathways is typically unknown in most biologic systems, to say nothing of subsequent good mathematical approximations of the resultant inter-network dynamics. The key point, similarly for ApEn, is that full model specification is not required to realize an effective discrimination strategy. Furthermore, of course, there is a paucity of general *multi*variate time-series statistical tools, discussed further below.

In addition to the evident means to potentially discriminate network aspects of systems, cross-ApEn allows us to now address the following critical, yet generic, network issue: are system changes primarily nodal (one-variable), or rather, path-

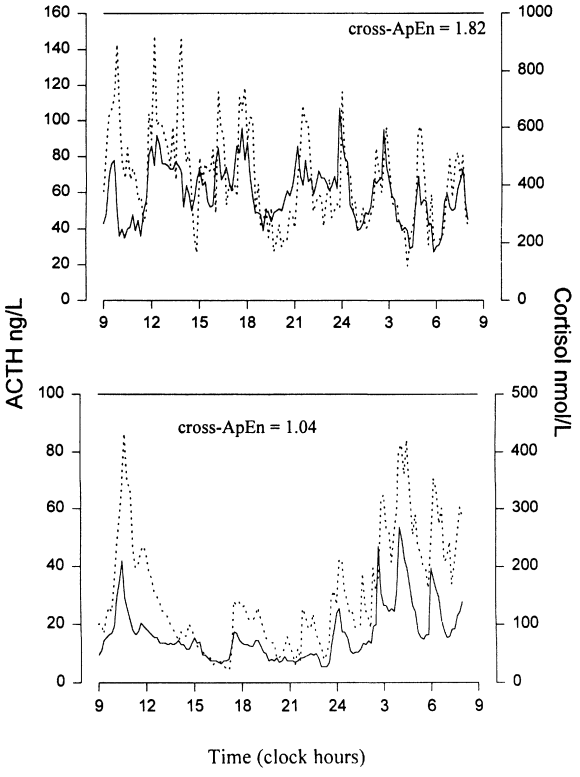

Fig. 3 Plasma concentrations of ACTH (dotted line) and cortisol (continuous line) in a female patient with Cushing's disease (upper panel) and a control subject (lower panel), each sampled at 10-min intervals for 24 h

way or central control alterations (multivariate)? An answer to this question is not only essential to basic system understanding, but also a prime determinant in choosing, e.g., therapy/intervention strategies to attempt to restore pathobiologic milieus to more normative settings. Also, given multiple node networks, we can successively probe pairwise, via cross-ApEn, to determine the weakest or altered (paired) links in the system. The precise definition, introduced in ref. ((42), Definition 5) is thematically similar to that for ApEn. Cross-ApEn has good statistical replicability for wide ranges of mathematical models and processes, similar to that for ApEn (40).

A representative example of the application of cross-ApEn to biological data is as follows. A study was performed to determine possible secretory irregularity shifts with aging within the LH-T hormone secretory axis (40). Serum concentrations were derived for LH and T in 14 young (21–34 yr) and 11 older (62–74 yr) healthy men. For each subject, blood samples were obtained at frequent (2.5 min) intervals during a sleep period. Although mean (and SD) of LH and T concentrations were indistinguishable in the 2 age groups, cross-ApEn was applied to the paired LH-T time-series. Older subjects exhibited greater cross-ApEn values (1.961 ± 0.121) compared to younger subjects (1.574 ± 0.249), $P < 10^{-4}$, with nearly 100% sensitivity and specificity, indicating greater LH-T asynchrony in the older group. Moreover and notably, no significant LH-T linear correlation (Pearson "R") differences were found between the younger and older cohorts, $P > 0.6$. Mechanistically, the results implicate (LH-T) network uncoupling as marking male reproductive aging, and quantifiable establishes the existence of a "partial male menopause."

Relationschip to other approaches

Statistics related to chaos

The historical development of mathematics to quantify regularity has centered around various types of entropy measures. Entropy is a concept addressing system randomness and predictability, with greater entropy often associated with more randomness and less system order. However, there are numerous entropy formulations, and many entropy definitions can not be related to one other (29). K-S entropy, developed by Kolmogorov and expanded upon by Sinai, allows one to classify *deterministic* dynamical systems by rates of information generation (20). It is this form of entropy that algorithms such as those given by Grassberger and Procaccia (17) and by Eckmann and Ruelle (9) estimate. There has been keen interest in the development of these and related algorithms over the last 15 years, since entropy has been shown to be a parameter that characterizes chaotic behavior (52).

Unfortunately, the K-S entropy was not developed for statistical applications, and has major debits in this regard. The original and primary motivation for the K-S entropy was to handle a highly theoretical mathematics problem, determining when 2 Bernoulli shifts are isomorphic. In its proper context, this form of entropy is primarily applied by ergodic theorists to well-defined theoretical transformations, for which no noise and an infinite amount of "data" are standard mathematical assumptions. Attempts to utilize K-S entropy for practical data analysis represent out-of-context application, which often generates serious difficulties, as it does here. K-S entropy is badly compromised by steady, (even very) small amounts

of noise, generally requires a vast amount of input data to achieve convergence (25, 59), and is usually infinite for stochastic (random) processes. Hence a "blind" application of the K-S entropy to practical time-series will only evaluate system noise, not underlying system properties. All these debits are key in the present context, since most physiological time-series likely are comprised of both stochastic and deterministic components.

ApEn was constructed along thematically similar lines to the K-S entropy, though with a different focus: to provide a widely applicable, statistically valid formula that will distinguish data sets by a measure of regularity (29, 35). The technical observation motivating ApEn is that if joint probability measures for reconstructed dynamics that describe each of two systems are different, then their marginal probability distributions on a fixed partition, given by conditional probabilities, are likely different. We typically need orders of magnitude fewer points to accurately estimate these marginal probabilities than to accurately reconstruct the attractor measure defining the process. ApEn has several technical advantages in comparison to K-S entropy for statistical usage. ApEn is nearly unaffected by noise of magnitude below r, the filter level, gives meaningful information with a reasonable number of data points, and is finite for both stochastic and deterministic processes. This last point allows ApEn the capability to distinguish versions of composite and stochastic processes from each other, while K-S entropy would be unable to do so.

There exists an extensive literature about understanding (chaotic) deterministic dynamical systems through reconstructed dynamics. Parameters such as correlation dimension (16), K-S entropy, and the Lyapunov spectrum have been much studied, as have techniques to utilize related algorithms in the presence of noise and limited data (3, 15, 22). Even more recently, prediction (forecasting) techniques have been developed for chaotic systems (5, 11, 54). Most of these methods successfully employ embedding dimensions larger than $m = 2$, as is typically employed with ApEn. Thus in the purely *deterministic dynamical system* setting, for which these methods were developed, they reconstruct the probability structure of the space with greater detail than does ApEn. However, in the general (stochastic, especially correlated stochastic process) setting, the statistical accuracy of the aforementioned parameters and methods is typically poor – they suffer what is denoted by statisticians as a 'curse of dimensionality', akin to a statistical model overfit. See refs. (29, 42), and especially Section VII and Fig. 4 of ref. (32) for further elucidation, both analytically and visually, of this operationally central point.

Furthermore, the prediction techniques (5, 11, 54) are no longer sensibly defined in the general context. Complex, correlated stochastic and composite processes are typically not evaluated, as they are not truly chaotic systems. The relevant point here is that since dynamical mechanisms of most biological signals remain undefined, a suitable statistic of regularity for these signals must be more "cautious", to accommodate general classes of processes and their much more diffuse reconstructed dynamics.

Generally, changes in ApEn agree with changes in dimension and entropy algorithms for low-dimensional, deterministic systems. The essential points here, assuring broad utility, are that (i) ApEn can potentially distinguish a wide variety of systems: low-dimensional deterministic systems, periodic and multiply periodic systems, high-dimensional chaotic systems, stochastic and mixed (stochastic and deterministic) systems (29, 39), and (ii) ApEn is applicable to noisy, medium-sized data sets, such as those typically encountered in biological time-series analysis. Thus ApEn can be applied to settings for which the K-S entropy and correlation dimension are either undefined or infinite, with good replicability properties as indicated above.

Complementarity to correlation and spectral analyses

Mathematically, the need for ApEn, and particularly for cross-ApEn, is clarified by considering alternative parameters that might address similar concepts. In comparing two distinct signals or variables (e.g., to assess a degree of synchrony), primary parameters that one might employ include the cross-correlation function, and the cross-spectrum (7), with single variable counterparts the auto-correlation function and the power spectrum.

Most importantly, the autocorrelation function and power spectrum, and their bivariate counterparts, are most illuminating in linear systems, e.g., SARIMA (seasonal autoregressive integrated moving average) models, for which a rich theoretical development exists (2). For many other classes of processes, these parameters often are much less effective at highlighting certain model characteristics, even apart from statistical considerations. This point is clearly illustrated in ref. ((40), Appendix), via study of a simple, yet representative model, which we denote as a "variable lag" pulsatile process. Similar limitations of the spectra and autocorrelation function are inherent to wide classes of processes. Notably, for many two-dimensional analogs of variable lag processes, and indeed for many two-dimensional systems in which no small set of dominant frequencies encapsulates most of the total power (i.e., for broad-banded spectra with few sharp peaks), the cross-spectrum and the cross-correlation function often will similarly fail to highlight episodicities in the underlying model and data, and thus fail

to highlight concomitant changes to such episodic components.

As a consequence of this, both for many empirical data sets and for complicated, composite models, ApEn and cross-ApEn frequently quantify more clearly time-series distinctions than do spectral and correlation assessments (both univariate and bivariate). This is illustrated in ref. (40), as noted above, in which older subjects had highly significantly greater cross-ApEn (LH-T) values than did younger subjects, while no significant LH-T linear correlation (Pearson "R") differences were found between the younger and older cohorts, either lagged or unlagged.

Conclusions and future direction

The principal focus of this article has been the description of ApEn, a quantification of serial irregularity, and its application to cardiologic time-series data. Several properties of ApEn facilitate its utility for such analysis: (i) ApEn can be applied to time series of 50 or more points, with good reproducibility; (ii) ApEn is nearly unaffected by noise of magnitude below a de facto specified filter level; (iii) ApEn is robust to outliers; (iv) ApEn is finite for stochastic, noisy deterministic and composite (mixed) processes, these last of which are likely models for complicated biological systems; (v) increasing ApEn corresponds to intuitively increasing process complexity in the settings of (iv); (vi) changes in ApEn have been shown mathematically to correspond to mechanistic inferences concerning subsystem autonomy, feedback, and coupling, in diverse model settings. The applicability to medium-sized data sets and general stochastic processes is in marked contrast to capabilities of "chaos" algorithms such as the correlation dimension, which are properly applied to low-dimensional iterated deterministic dynamical systems. The potential uses of ApEn to provide new insights when applied to cardiologic data are thus considerable, from a complementary perspective to that given by classical statistical methods.

Moreover, we also proposed cross-ApEn, a related measure of two-variable asynchrony, as a measure of potential interest, especially, e.g., to paired heart rate–respiratory dynamics. Applying cross-ApEn, we can directly assess network, and not just nodal, evolution, under different settings – e.g., to directly evaluate uncoupling, and/or changes in feedback and control.

Applications to multiple heart rate studies confirmed that ApEn consistently detected subtle shifts in heart rate rhythmicity, with greater regularity (lower ApEn) clinically corresponding to compromised physiology in all settings. A mechanistic interpretation, mathematically established elsewhere and consistent with the heart rate studies, is that such greater regularity typically manifests compromised network development or performance.

In most of the studies discussed above, R-R intervals ('heart rate') were the derived measure of choice from the ECG on which subsequent time-series analysis (ApEn or otherwise) was performed. It would be interesting, and potentially worthwhile, to perform ApEn on other interval sequences, such as Q-T segments, to determine if shifts in their patterns over time corresponded to and predicted physiologically important correlates. Similarly, ApEn could be applied to sequences of interbeat times between ectopic beats, to determine whether the timing of such, and not just the frequency, has clinical significance.

Finally, an inadequately explored area of important research would be that of drug effects on the complexity or irregularity of cardiovascular dynamics. ApEn could be used to discern the effects of, e.g., cocaine, opiates, methadone, alcohol and tobacco, on cardio-respiratory data; and it could be employed to assess response to anesthetics, including 'depth of anesthesia', via either or both of ECG/heart rate or EEG analyses.

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