# MULTI-OBJECTIVE PHYSIOLOGICAL INDICATORS BASED ON COMPLEMENTARY COMPLEXITY MEASURES: APPLICATION TO EARLY DIAGNOSTICS AND PREDICTION OF ACUTE EVENTS

**VALERIY V. GAVRISHCHAKA**
Department of Physics, West Virginia University, Morgantown, WV 26506 USA
gavrish@verizon.net

**MARK E. KOEPKE**
Department of Physics, West Virginia University, Morgantown, WV 26506 USA
Mark.Koepke@mail.wvu.edu

**OLGA V. SENYUKOVA**
Department of Computational Mathematics and Cybernetics, Moscow State University, Moscow, Russian Federation
olsen222@yandex.ru

**ANASTASIYA I. KRYUCHKOVA**
Association of Surgical Technologists, USA
anastasiakrioutchkova@yahoo.com

***ABSTRACT***
Advancements in clinical, portable, and wearable equipment for real-time collection of physiological data provide new opportunities for computerized diagnostics of developed pathologies, early detection of emerging abnormalities, and prediction of acute and critical events. However, many conceptual and algorithmic challenges for robust quantitative modeling in such applications remain unresolved. Variability analysis of physiological time series provides a generic framework for quantification of normal and abnormal states and their discrimination. Unfortunately, in many clinically significant cases it is hard to achieve robust "normal-abnormal" classification using this framework or other established diagnostic modalities. Recently, we have demonstrated that many problems in heart rate variability (HRV) analysis could be overcome when several complementary nonlinear dynamics (NLD) indicators (complexity measures) are combined using boosting-like algorithms. Such generic meta-indicators are capable to detect both single abnormalities irrespective of their specific type, and conditions specified by complex combination of different pathologies. Here we argue that aggregated probability-like output of these multi-component models could be effective for more detailed quantification of psycho-physiological states. These robust state representations could be used as early signals of emerging abnormalities and other negative physiological changes as well as for real-time prediction of acute and critical events. In addition, we propose some extensions to HRV analysis and possible ways of its application to other physiological channels
***KEY WORDS***
Ensemble learning, Boosting, Physiological Indicators, Cardiac Diagnostics, Heart Rate Variability, Nonlinear dynamics, Complexity Measures

## 1. INTRODUCTION

Technological advancements is clinical, portable, and wearable devices for real-time collection of physiological data provide new opportunities for computerized diagnostics of developed pathologies, early detection of emerging or transient abnormalities, and accurate prediction of acute and critical events. However, many conceptual and algorithmic challenges for accurate and robust quantitative modeling in such applications remain unresolved. Typical limitations of pure data-driven statistical and machine learning frameworks include critical sensitivity to data incompleteness, operational instability, and poor interpretability. In addition, many diagnostic features and rules used in practice are formulated for developed forms of particular abnormalities. They cannot be readily used for early warning of emerging abnormalities of yet unknown origin or for diagnostics of conditions specified by complex combination of different pathologies. The majority of diagnostic features used by cardiologists are based on local patterns extracted from electrocardiogram (ECG) waveforms. However, these features may not be effective in the early stage of developing cardiac abnormalities as well as for clinically significant pathologies lacking specific ECG signatures.

Human organism is a complex adaptive system. Signal variability analysis provides a generic non-invasive technology for evaluation of the overall properties of a complex system. The association between altered variability and illness is ubiquitous [1-4]. One of the most common applications of this principle is heart rate variability (HRV) analysis which is known to play an important role in cardiac diagnostics [1-4]. HRV indicators calculated from beat-to-beat (RR) time series offer not only a complementary diagnostic modality but also potential detection of subtle dynamical changes in the early stages of emerging pathologies. Analysis of RR data is also significantly more noise-tolerant compared to waveform analysis. This is especially important for data collected by portable and wearable systems.

Although variability analysis combines many desirable characteristics, sensitivity of linear HRV indicators to data artifacts and non-stationarity, as well as long-period requirements for more accurate and stable nonlinear dynamics (NLD) measures lead to many challenges in practice. Nevertheless, in our recent works we have demonstrated that NLD indicators could preserve significant part of their discriminative abilities even for short periods (down to several minutes) [5,6]. More importantly, we have shown that accuracy of "normal-abnormal" classifiers based on different NLD measures could be significantly increased by boosting-like ensemble learning methods [5,6]. This approach allows discovering generic meta-indicators capable of detecting both single abnormalities irrespective of their origin, and conditions specified by complex combination of different pathologies.

In this paper, we argue that aggregated probability-like output of these multi-component meta-models could be effective for more detailed and robust quantification of psycho-physiological states. We demonstrate how these state representations could be used as early signals of emerging abnormalities and other negative physiological changes (e.g., overtraining in professional sports) as well as for real-time prediction of acute and critical events. In addition, we propose some extensions to HRV analysis and possible ways of its application to other physiological channels. Several supporting illustrations based on MIT-BIH data (www.physionet.org ) are presented.

## 2. CHALLENGES OF EARLY DIAGNOSTICS AND REAL-TIME PREDICTION OF ACUTE EVENTS

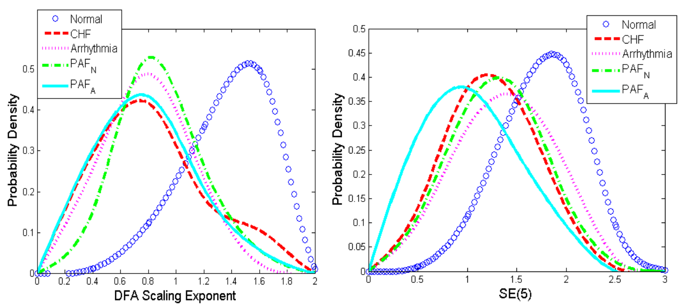
Traditional diagnostics could typically reveal only the known localized patterns while information from long-range multi-scale correlations in the dynamics of ECG or other physiological time series is ignored. However, measures based on such subtle changes in dynamics may be sensitive indicators of an emerging abnormality or hard-to-detect pathology. HRV analysis offers a set of measures that are sensitive to such changes in heart rate dynamics and can provide complementary and alternative insight in cardiac diagnostics [1-4].

Although, only linear indicators are mainly used in modern HRV analysis [4], NLD methods provide more accurate modeling framework for adaptive biological systems with multiple feedback loops [1-3,7]. For example, NLD-based measures are much less sensitive to data artifacts, non-stationarity, and to changes in patient activity [1]. However, formal requirements for NLD indicator calculations specify necessity of long RR segments (~ several hours) [1-3,7]. Such restrictions could drastically limit effectiveness of HRV analysis in many applications where ability to work with short RR time series (down to several minutes) is critical. The range of these applications varies from express diagnostics to detection of transient abnormalities and prediction of acute events.

Well-known complexity measures based on detrended fluctuation analysis (DFA) [8] and multi-scale entropy (MSE) [9] can be used to illustrate these problems that are also relevant for other NLD and linear indicators. DFA was proven to be useful in revealing the extent of long-range correlations in time series. Peng et al. found that DFA scaling exponents $b$ computed from ~2-hour or longer RR segments provide distinctive clustering of the normal and congestive heart failure (CHF) cases, however, with noticeable overlapping [8]. DFA can be also extended for multi-fractal analysis (MFA) with additional diagnostic signatures.

MSE method [9] has been introduced to resolve limitations of traditional single-scale entropy measures. Multiple coarse-grained time series are constructed by averaging the data points within non-overlapping windows of increasing length. Next, sample entropy (SE) is calculated for each such time series and plotted as a function of the scale (aggregation) factor. Typical types of MSE behavior have been summarized in [9]. Different features of MSE curves could be used for separation of normal and pathological cases. One of the simplest is the slope $b$ of MSE curve [9]. However, although these features could provide statistically significant separation between different classes, the required long time periods (~ 24 hours) and significant overlapping of the classes pose the same practical problems as with DFA.

Recently, we have demonstrated that NLD indicators, usually considered for long periods, can preserve significant part of their stylized facts and discriminative abilities for much shorter periods [5,6]. However, increasing overlapping between classes creates serious obstacles for the direct application of such indicators. These facts are illustrated in figure 1, where we present probability density distributions (PDF) of DFA and MSE measures calculated for much shorter RR segments than in the original publications [8,9]. For this purpose, we used RR data from 52 subjects with normal sinus rhythm, 27 subjects with congestive heart failure, and 48 subjects with different types of arrhythmia (MIT arrhythmia database) from www.physionet.org. Up to 24 hours of RR data for normal and CHF subjects are available which results in ~$7.3\times10^6$ of total number of beat-to-beat intervals. In addition, up to 30 min of RR data are available for each subject with arrhythmia. We have also added to MIT arrhythmia database 78 intervals (each of ~30 min) from patients with supraventricular arrhythmias and 106 records (each ~30 min long) from patients with paroxysmal atrial fibrillation (PAF). Half of PAF records immediately precedes atrial fibrillation (AF) event ($PAF_A$) and the other half is taken far from any such event ($PAF_N$). Since, in our analysis, we do not use PAF data in training phase, we combine both in-sample and out-of-sample data provided for the Computers in Cardiology Challenge 2001 (www.physionet.org).




(a) (b)

Fig.1 Distribution of (a) DFA scaling exponent for 4<=n<=16 and (b) SE(5) derived from short RR time series (103 beats) of healthy (normal) subjects and patients with CHF, arrhythmia, and PAF (A– data taken close to AF event and N – far from any such event)

All DFA and MSE calculations for figure 1 use the same parameters as in the original publications [8,9] except RR segment length: $10^3$ beats or ~15min instead of at least several hours. Although the average values from figure 1 indicate reasonable separation between normal and variety of abnormal classes even for short RR time series, the PDFs of DFA and MSE measures demonstrate significant overlapping between normal and abnormal classes. Figure 1 also illustrates that, although various abnormalities have quite distinct dynamical signatures, as a group they are still significantly different from signatures of healthy subjects. This suggests possibility of universal HRV classifiers capable of distinguishing between normal cardiac condition and wide range of abnormalities without specification of their origin. However, due to significant overlapping between classes, combination of complementary indicators using boosting-like algorithms could be crucial to achieve practically acceptable performance [6].

Figure 1 also shows that, while PDFs of several abnormality types are quite distinguishable from the normal PDF, the separation between different abnormalities themselves is much more ambiguous. For example, discrimination between $PAF_N$ and $PAF_A$ cases, that is required for prediction of AF event, could be significantly more difficult than just PAF screening, where a normal case needs to be distinguished from either $PAF_N$ or $PAF_A$ cases. Therefore, more subtle and sensitive representations of physiological states are needed. As discussed in the next section, the probability-like output of the boosting-discovered meta-classifiers could be effective for this purpose.

## 3. QUANTIFICATION OF PHYSIOLOGICAL STATES BY MULTI-TYPE COMPLEXITY MEASURES AND ITS APPLICATIONS

Significant improvements in accuracy and stability can be achieved by combination of complementary complexity measures. Adaptive boosting and similar ensemble learning algorithms combine many desirable features including capability of reducing both bias and variance parts of the model error [15,16]. Therefore, boosting can be applied to the pool of well-understood low-complexity models to produce an interpretable combined model with significantly higher accuracy and stability as discussed in [17]. Moreover, boosting tries to maximize the margin to ensure good out-of-sample performance [15,16].

A typical boosting algorithm such as AdaBoost [15,16] for the two-class classification problem starts with equal and normalized weights for all training data. Base classifiers, $h_t(x)$, are trained using weighted error function and the best one is chosen at each iteration $t$. Here $x$ is an input vector. Data points misclassified by the current best model are penalized by the weight increase for the next iteration. Therefore, on each iteration, the algorithm is focused on more hard-to-classify samples. The final meta-model, given below, classifies the unknown sample as class +1 when $H(x) > 0$ and as -1 otherwise:

$$H_T(x) = \sum_{t=1}^{T} a_t h_t(x) \qquad (1)$$

Here, $a_t$ are combination coefficients obtained, and $T$ is the total number of iterations. Regime adjustments together with important regularization procedures can be also introduced to the original boosting algorithm in several ways. One of them is input-dependent boosting [18], where instead of constant combination coefficients $a_t$, one makes them input dependent with a nonzero regularization parameter, $l$:

$$H_T(x) = \sum_{t=1}^{T} a_t e^{-|l H_{t-1}(x)|} h_t(x) \qquad (2)$$

This allows the algorithm to adapt itself to different regimes – or regions of a feature space.

A natural choice of base models could be low-complexity base classifiers where each of them uses a small subset of the available complexity measures $b_i, i = 1,\ldots,N$ . In our case $b_i$ may correspond, for example, to DFA scaling exponent or a slope of MSE curve. Our empirical analysis indicates practicality and robustness of base classifiers based on just a single measure $b_i$:

$$y = h(b_i[p_i], g) . \quad (3)$$

Here $g$ is a threshold level (decision boundary) and $p_i$ is a vector of parameters of the chosen measure (e.g. DFA or MSE parameters). Applying boosting steps to a set of such base classifiers with different measures $b_i$ and optimizing over $(p_i,g)$ on each boosting iteration, we obtain a meta-classifier (Eq.1 or 2).

Multiple boosting runs with different objective functions, regularization parameters, different subsets of base classifiers and other varying options could produce a large collection of comparable multi-component meta-classifiers. It is beneficial to use a set of multi-objective performance measures to quantify accuracy gain achieved by boosting relative to a single best classification model. Such performance measures could also be used in decision-making process when a single meta-classifier is chosen for a particular application.

For a single classifier, detection (hit) rates are plotted vs false alarm rates to obtain ROC (Receiver Operating Characteristic) curve that clearly summarizes the model effectiveness: the larger is ROC-curve's shift towards the upper left corner from the diagonal, the better is classifier. Although the formal decision boundary of the meta-classifier $H(x)$ (Eq.1 and 2) constructed by boosting is zero, one can still vary the decision boundary around zero to obtain ROC curve for such a multi-component classifier. Such ROC curves could be conveniently used to choose a single decision boundary with an appropriate combination of detection and false alarm rates. For a collection of meta-classifiers with comparable performance, one could combine a collection of ROC curves from different meta-classifiers into one set (single curve) of the non-dominated solutions similar to Pareto optimal front considered in multi-objective optimization frameworks [19]. The only difference from a regular ROC curve is that different points on the curve may correspond to different meta-classifiers.

First, using these multi-objective performance measures, we expand and provide more detailed quantification of our previous results [6]. For this purpose about 1/3 of all data for normal and CHF subjects, and 1/2 of arrhythmia data employed in figure 1 have been used for training and the rest for testing. All the discussed results are based on out-of-sample data. We found that applying boosting to the base DFA and MSE models (Eq.3), it is possible to discover multi-component meta-classifiers with attractive multi-objective performance measures even for very short RR segments (256 beats or <5min). Boosting-caused improvements are quite noticeable even though only a small subset of possible indicators from just two types of complexity measures (DFA and MSE) has been used. For example, CHF detection rate of the meta-classifier could be increased by up to 5-10% for a given false alarm rate, while false alarm rate can be decreased by more than 10% for a given detection rate compared to the best single model.

More challenging and practically important problem is detection of multiple abnormalities and their complex combinations. Results summarized in figure 1 suggest that, despite variations of signatures of different abnormalities, all of them are significantly different from the normal case. However, direct extensions such as multi-class classification framework or collection of two-class classifiers specialized on a particular abnormality face several serious problems. For example, only abnormalities with significant amount of clearly diagnosed training data could be considered. Therefore, valuable information from less frequent and novel abnormalities as well as complex cases with combination of different pathologies or with non-specific diagnoses will not be taken into account. In turn, such classifier(s) could easily become inaccurate and unstable when dealing with examples that are not directly associated with specific abnormality types used in training.

We found that it is feasible to discriminate between normal condition and multiple abnormalities using two-class classification framework. Such an approach is tolerant to training data with vaguely specified or non-specific diagnoses, data incompleteness for certain well-known and novel abnormalities, and to complex cases of co-existing pathologies. "Normal-abnormal" universal classifiers obtained in such a way could be employed for robust detection of abnormalities irrespective of their specific type or in cases of complex combination of different pathologies. This conclusion is supported by the fact that the same meta-classifiers can produce comparable ROC curves for CHF-normal, arrhythmia-normal, and PAF-normal cases. A practical decision-making procedure may benefit from aggregated performance metrics in the form of a single generalized ROC curve where detection rates for several abnormalities are combined by either equal averaging or with weights according to prior probabilities of these abnormalities. For example, a generalized ROC curve with detection rate of CHF and arrhythmia equally averaged is shown in figure 2a. Significant improvement of the boosting-based meta-classifier compared to a single best model is obvious even though only two types of measures are used.

Figure 2a and our previous results [6] clearly illustrate that diversity of the base HRV indicators could be efficiently exploited by boosting to improve performance of the final meta-indicators. Addition of other types of complexity measures and base models would further increase accuracy of such multi-component indicators.

More diversity and complementary information content could also be introduced by considering long-range correlations of other ECG patterns besides RR intervals. Here, we present a preliminary illustration of meta-classifier performance gain achieved when a derivative of RR time series is used in addition to the original RR time series. It was pointed out in [20] that application of NLD measures, typically used for inter-beat intervals $B(i)$, to the derivative time series $(B(i+1)-B(i))$ could improve accuracy of the original indicators. To determine boosting-based accuracy gain due to diversity of input time series and not model-type diversity, we consider base models (Eq.3) with only MSE indicator but with two types of inputs: original RR time series and its derivative. Figure 2b shows generalized ROC curve with detection rate of CHF and arrhythmia equally averaged for the meta-classifier with original RR input (solid curve) and with mixture of two types of input. Significant performance improvement is obvious. In practice, it is natural to use model and input diversification simultaneously to achieve further accuracy and stability gains.

In addition to direct classification for express diagnostics, the time series of an aggregated probability-like output of the meta-model (Eq. 1 or 2) could be used in sensitive personal monitoring for early detection of positive or negative psycho-physiological changes. For example, due to significantly reduced noise compared to single HRV measures, such an aggregated quantification of a psycho-physiological state could be used for early detection of treatment effects, thus allowing optimization of the personalized treatment strategy. Another important application could be robust and convenient detection of athletes' overtraining, since existing HRV indicators, although informative, often produced unstable and ambiguous results in practice [21].

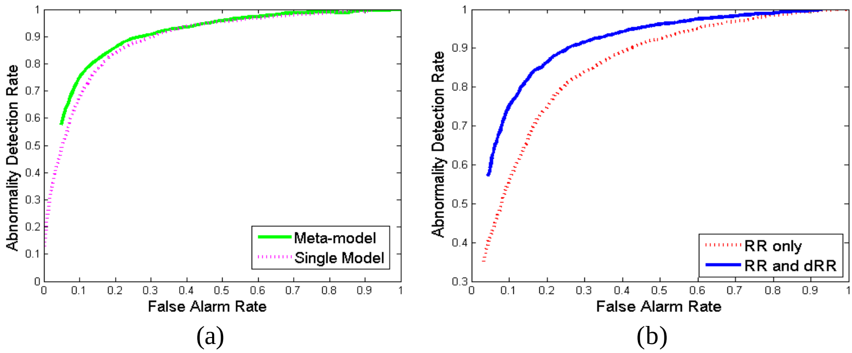
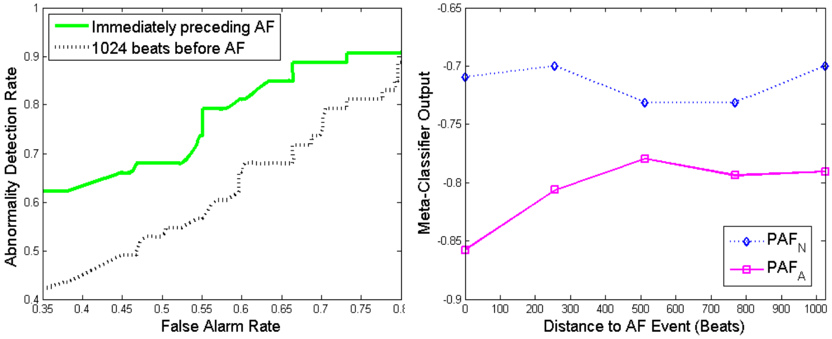



Fig.2. ROC curves – equally averaged detection rate for CHF and arrhythmia vs false alarm rate: (a) Best single classifier (solid line) and boosted meta-classifier (dotted line), where DFA and MSE are calculated from RR data; (b) MSE-only boosted meta-classifiers, where only RR data (solid line) and combination of RR and differentiated RR data (dotted line) are used

Reliable prediction of AF, spontaneous ventricular fibrillation (VF) and tachycardia (VT), and other acute cardiac events is very important for applications in smart pacers and defibrillators. This set of problems is more challenging than those discussed so far.

Direct usage of probability-like output of the meta-classifier could be quite reliable for various cases where one can see a consistent quasi-stationary shift of the meta-indicator range. However, prediction of an acute event involves detection of subtle and transient precursors before the actual state change where effective data analysis could often be limited to short segments before the event. In addition, the amount of reliable data for real life-threatening events is often more limited compared to data for different pathologies or other persistent physiological conditions. However, our analysis indicates that aggregated output from the meta-classifier trained on multi-abnormality data could be an effective predictor of acute cardiac events. It can be used without any additional re-training on the limited data containing examples of such events.




(a) (b)

Fig.3 (a) ROC curves ($PAF_A$ detection rate vs $PAF_N$ false alarm rate) for 512-beat RR segments: 1024 beats before AF start (solid line) and immediately preceding AF start (dotted line); (b) Meta-classifier output (computed from 512-beat RR segments) averaged over all $PAF_A$ samples (solid line) and all $PAF_N$ samples (dotted line) vs distance (in beats) to AF event

To illustrate the above conclusions, we used one of meta-classifiers trained on CHF and arrhythmia data and applied it to discriminate between $PAF_A$ and $PAF_N$ data which can be used for AF event prediction. We found that if all of 256 or 512-beat segments from ~1500 beats available for each $PAF_A$ and $PAF_N$ case are used, the corresponding ROC curve, i.e. $PAF_A$ detection rate vs $PAF_N$ false alarm rate, is only slightly above the diagonal indicating insignificant separability. However, more detailed analysis, summarized in figure 3a, shows that accuracy of AF prediction crucially depends on the distance to the event starting point. For example, ROC curve for 512-beat segment immediately preceding AF event is well above the diagonal, while prediction accuracy from the segment 1000-beats before the event is not acceptable.

Further confirmation of the localized nature of potential AF precursors is given in figure 3b. Here, meta-indicator outputs on all $PAF_A$ and $PAF_N$ 512-beat overlapping RR segments with different distances to AF event start are computed and averaged. Separation between these classes increases closer to AF event. Results from figure 3b also suggest that, instead of using a single output from the meta-classifier, one can construct a short time series of these outputs computed on sliding windows of RR data and look for more sophisticated temporal patterns that may increase prediction rate of the AF events. We found that even simple analysis of such time series could increase prediction rate by several percent compared to a single number immediately preceding the event. We also obtained qualitatively similar results for VT and VF event prediction using spontaneous ventricular tachyarrhythmia database from www.physionet.org. Further research on this topic is warranted.

## 4. POSSIBLE EXTENSIONS OF THE PROPOSED FRAMEWORK

Typical problems and their solutions discussed here are relevant for other physiological channels and non-cardiac abnormalities as well. For example, DFA and other NLD measures computed from EEG time series could be employed in the construction of indices for depression severity [10], epileptic seizure prediction [11], classification of mental tasks (applicable in brain-computer interface systems) [12], anesthesia depth assessment [13], early detection of acute cerebral ischaemia [14], and many others. Therefore, problems and their potential solutions discussed here in the context of ECG-based diagnostics could be directly relevant for EEG and other physiological channels as well.

Another promising source of diversity is generalization of HRV analysis itself. Indeed, only RR data extracted from the original ECG time series is used to calculate HRV indicators. Although RR intervals provide a rich and noise-tolerant information channel, other ECG local patterns often offer important complementary information given the low-noise original time series. Existing HRV indicators could be used to study long-range temporal dependencies of various local ECG patterns in addition to just RR intervals. This generalized HRV approach is very different from the standard ECG waveforms analysis and it could provide early warnings based on long-range correlations when pronounced abnormal changes in local waveform patterns are not yet formed.

In addition to aggregated probability-like output of proposed multi-component meta-classifiers, non-aggregated information extracted from the internal structure of such meta-classifiers could be also essential in certain complex and/or rare cases.

## 5. CONCLUSIONS

We have shown that boosting-based framework could be effectively used for the discovery of universal physiological meta-indicators from complementary NLD complexity measures. Such indicators are capable to detect both single abnormalities irrespective of their specific type, and conditions specified by complex combination of different pathologies. In addition, probability-like output of these multi-component models could be effectively used as early signal of emerging abnormalities and other physiological changes as well as for real-time prediction of acute and critical events. Generalization of HRV analysis by considering long-range temporal dependencies of various local ECG patterns is also suggested. The proposed framework could also prove to be effective for other physiological channels (e.g., EEG) and non-cardiac abnormalities.

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