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SYSTEMS-LEVEL QUALITY IMPROVEMENT

K – Shrinkage Function for ECG Signal Denoising

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Abstract

ECG signals is a graphical way of recording the electrical actions of the heart for the various diagnostic purposes. ECG signals are affected by various noises such as Electrode Contact, Baseline Wandering, Motion artifact, Power-line interference, Muscle Contractions, and Electrosurgical noise during data acquisition. Denoising is a technique which is used for removing the noise in ECG signals which keeps the useful information. In this paper, a new category of Wavelet shrinkage methods is proposed. The white Gaussian noise is mixed with the ECGs for simulation and tested with the new class of shrinkage function and is compared with the other wavelet shrinkage functions such as hard and soft shrinkage. The performance measures such as Signal to Noise Ratio (SNR) and Percent Root mean – square Difference (PRD) etc. are used to examine the performance of various shrinkage functions. The experimental result shows that it gives better MSE over conventional shrinkage functions.

Keywords Electrocardiography (ECG) · Interference · Signal denoising · Signal to noise ratio (SNR) · Wavelet transforms

Introduction

ECG signal is a way of recording bioelectric currents generated by the heart and it is useful for various diagnostic purposes. From the recording, the diagnostic information is extracted which requires proper classification of waveform such that preserving the original signals and higher noise can be attenuated. Noises present in the ECG signal are Electrode Contract Noise, Base-line Wander interference, Power-line interference, Muscle – contraction and Electrosurgical interference [1].

Wavelets are used to decompose the ECG signals, we get lower frequency and higher frequency sub-bands. The details available in the high frequency sub-bands are less which can be removed from the signal without affecting it and it is associated with noise also. These sub-bands are removed by using a threshold value and setting it as zero when the magnitude is smaller than the thresholds. It will become the basis for thresholding. Threshold value can be used to distinguish significant and insignificant data.

The different method of shrinkage methods are examined in this paper. The shrinkage function using Wavelets was first introduced by Johnstone and Donoho (1997) followed by the work of Breiman (1995) and Gao (1996). Johnstone and Donoho have developed it for recovering function from the noisy data [2]. Soft shrinkage is performed in an iteration manner hence it achieves good SNR as well as data compression and increases computational efficiency. It shrinks all the large coefficients by the threshold value λ towards zero which lead to a bigger bias and less sensitive for the small changes in the data. Hard shrinkage become unstable due to the small fluctuations in data.

The hard shrinkage method is a preprocessing technique that will determine the functions from the noisy data. It is a keep or kills procedure and is more intuitively appealing. It seems to be natural but pure noise coefficients may pass through it and appear as an infuriated mark on the signal by using the fixed thresholding concept.

Donoho and Johnstone proposed the hard and soft shrinkage function [2] as:

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$$\delta_\lambda^H = \begin{cases} 0, & |x| \le \lambda \\ x, & |x| > \lambda \end{cases} \quad (1)$$

$$\delta_\lambda^S = \begin{cases} 0, & |x| \le \lambda \\ x-\lambda, & x > \lambda \\ x+\lambda, & x < -\lambda \end{cases} \quad (2)$$

Where $\lambda \in [0, \infty]$ – threshold value.

The shortcoming of hard and soft shrinkage function are overcomes by the general firm shrinkage. Bruce and Gao [3] introduced a general Firm shrinkage function $\delta_{\lambda 1,\lambda 2}(x)$ [3–5]. It uses two threshold values $\lambda 1$ and λ_2: x value is close to the lower threshold λ_1, $\delta_{\lambda 1,\ \lambda 2}(x)$ will behave as the soft shrinkage and the value of x above the threshold $\lambda 2$, $\delta_{\lambda 1,\ \lambda 2}(x)$ will behave as the hard shrinkage. The major drawback of Firm shrinkage is threshold values required are two. Note that hard shrinkage, with $\lambda 1 = \lambda 2$, and soft shrinkage, with $\lambda 2 = \infty$, are limiting cases of Firm shrinkage [3–5].

$$\delta_{\lambda_1,\lambda_2}(x) = \begin{cases} 0, |x| \le \lambda_1 \\ sgn(x)\, \dfrac{\lambda_2(|x|-\lambda_1)}{\lambda_2-\lambda_1}, \lambda_1 < |x|\lambda_2 \\ x, |x| > \lambda_2 \end{cases} \quad (3)$$

Breiman (1995) have proposed the non-negative shrinkage function [6], which has good trade-off between the soft and hard shrinkage models. Due to the shortcoming of step-wise model, it is applied to subset regression model. The non-negative function is continuous and less sensitive than hard shrinkage for the small changes in the data and provide minimum bias comparing to soft shrinkage [7]. When the original signal has many small nonzero coefficients then the garrote function will have lower prediction error. Breiman (1995) proposed the functions as follows:

$$\delta_\lambda^G = x\left\{1-\left(\frac{\lambda}{x}\right)^2\right\} = \begin{cases} 0, |x| \le \lambda \\ x-(\lambda^2/x), |x| \le \lambda \end{cases} \quad (4)$$

S. Poornachandra and N. Kumaravel have proposed hyper trim shrinkage $\delta_\lambda^{hyp}(x)$ [8, 9] which is based on universal threshold [2] and α-trim threshold [10]. It is a non – linear model and based on the hyperbolic functions. It provides an improvement in bias and variance estimation given by Andrew and Bruce (1996). The distribution characteristics of hyperbolic function is related to the basic shrinkage distribution among its family. It provide better MSE and it is a function of continuous derivative.

$$\delta_\lambda^{hyp} = \tanh(\rho * x)(|x|-\lambda)_+ \begin{cases} 0, |x| > \lambda \\ \tan(\rho * x), |x| > \lambda \end{cases} \quad (5)$$

Where.

ρ Boundary contraction parameter.

S. Poornachandra and N. Kumaravel proposed sub-band adaptive shrinkage function $\delta_\lambda^{SA}(x)$ [11] and which is based on the hyperbolic behaviour and perform well than the other shrinkage models.

$$\delta_\lambda^{SA} = \begin{cases} \rho \dfrac{\left[1-\lambda_j^{-2\lambda_j x}\right]}{\left[1+\lambda_j^{-2\lambda_j x}\right]}, |x| \ge \lambda_j \\ 0, |X| < \lambda_J \end{cases} \quad (6)$$

$$\rho = \frac{\Delta}{\max|x|} \quad (7)$$

Where.

ρ Boundary contraction parameter.

It uses sub-band dependent thresholding [10, 12] method for better retrieval of the signal when tested with the real time ECG signal. The value of ρ is depend on the boundary attaining parameter Δ. The value of Δ are used for retaining the exponent behaviour of shrinkage models outside the distribution curve and results will depend on the replicated trials. If the value of parameter Δ can be increased we will get fractional change in SNR value.

Ustundag and Gokbulut (2012) proposed the fuzzy based thresholding method for denoising weak ECG signal using Wavelet analysis [12]. The fuzzy s-function can be used to construct the thresholding concept and it can be defined as:

$$f(x;a,b) = \begin{cases} 9, x \le a \\ 2\left(\dfrac{x-a}{b-a}\right)^2, a \le x \le \dfrac{a+b}{2} \\ 1-2\left(\dfrac{x-b}{b-a}\right)^2, \quad \dfrac{a+b}{2} \le x \le b \\ 1, x \ge b \end{cases} \quad (8)$$

Where a and b identifies the slope of the curve and the curve is based on the mapping on the vector x.

Fuzzy logic based thresholding for hyper shrinkage [13] was proposed by Saranya and Poornachandra which will improve the SNR values. Fuzzy Logic can be used for the uncertainty of information and it can express as a good mathematical concept.

The membership function of fuzzy logic can be defined as each point of input space is generalize into a value between 0 and 1. Fuzzy logic based thresholding for Sub-band adaptive shrinkage was proposed by selvakumarasamy and

Poornachandra which will improve the SNR values [14]. The denoising based on Wavelet shows greater advantages but the drawback is discontinuities and it illustrate the pseudo-Gibbs phenomenon [15].

The Genetic Optimized Wavelet Threshold (GOWT) [16] embrace a general quadratic function and it improve the versatility of denoising method for the various noisy signals. The GA was used to optimize the quadratic function. Quadratic curve thresholding function (QCTF) is expressed as:

$$y_q = \begin{cases} 0 \ |x| < \lambda \\ ax^2 + bx + c \ \lambda \le |x| < \lambda_e \\ x \ |x| \ge \lambda_e \end{cases} \tag{9}$$

here, a, b, and c – The coefficients of 0quadratic curve .

When the value of $\lambda_e \to \lambda$, then the QCTF will function as hard thresholding and for values of $\lambda_e \to +\infty$ is a soft thresholding function. The equations are expressed as:

$$0 = a\lambda^2 + b\lambda + c \tag{10}$$

$$\lambda_e = a{\lambda_e}^2 + b\lambda_e + c \tag{11}$$

After simplification, b and c is given by a and λ_e :

$$b = \frac{\lambda_e}{\lambda_e - \lambda} - a(\lambda_e - \lambda) \tag{12}$$

$$c = \lambda\lambda_e \left[\frac{1}{\lambda - \lambda_e} \quad + a \right] \tag{13}$$

The curve end point λ_e and curve coefficient a are the important parameters for the performance of QCFT. For recovering the original signal, the optimal parameters value in QCTF is very important.

The outline of this article is organized as: Section 2 describes the introduction to Wavelets. Section 3 gives a brief about the threshold function. The new proposed function is discussed in section 4. Section 5 report the results of the proposed function. The final section gives the conclusion.

Introduction to wavelet transform

Wavelets has flexible environment to analyze the non-stationary signals because of fast computational algorithms. Wavelet means "Small Wave" [15]. The Wavelet function generally refers either to orthogonal or nonorthogonal Wavelets [17, 18]. The uses of orthogonal basis are referring to a discrete WT but the nonorthogonal basis can be used with either discrete WT or continuous WT. In the Wavelet decomposition, the main information in the signal of low frequencies are contained in the approximation sub-bands and other information with noisy components are available in the detail sub-bands [19].

WT can be defined as:

$$W(s, \tau) = \int f(t) \varphi_{s,\tau}(t)\, dt \tag{14}$$

Where $\varphi_{s,\tau}(t)$ – mother Wavelet.

Wavelets are formed from the basic function $\varphi_{s,\tau}(t)$, using translation and scaling:

$$\varphi_{s,\tau}(t) = \frac{1}{\sqrt{s}}\, \varphi\left(\frac{t-\tau}{s}\right) \tag{15}$$

Where s and τ are scaling and translation parameter [19]. Wavelets has the following advantages [20, 21]: 1. The Wavelet filters is computationally fast; 2.It can support wide analysis in the low frequency component and narrow analysis in the high frequency component; 3. Wavelets are used to segregate the fine details and coarse details in the signal; 4. The fewer coefficients of wavelet is enough to get good approximation for a given function.

Threshold function

The shrinkage rules are used to determine threshold values. There are various threshold selection rules such as Rigrsure, Sqtwolog, Heursure, Minimax, Universal and Alpha – trim [22]. Rigrsure threshold is an adaptive threshold rule and it depends upon the unbiased estimation. It can be defined as

$$R(t) = \left(1 - \frac{t}{N}\right) y(t) + \frac{1}{N}\left(N - 2t - \sum_{i=1}^{t} y(i)\right) \tag{16}$$

$$T = \sqrt{\min R(t)} \tag{17}$$

Where.

x(t) is original sequence and t = 1,2,…..N.

Sqtwolog can be obtained by multiplying by a factor of log and it is called as fixed form threshold. This rule is expressed as

$$T = \sqrt{2\log N} \tag{18}$$

Heursure is a combination of two threshold rules: Rigsure rule and Sqtwolog rule. Minimax rule can be fixed threshold which yields minimax performance for an ideal procedure [20, 21]. It can be expressed as:

$$T = \begin{cases} \sigma\,(0.3936 + 0.10829\log_2 N), & N > 32 \\ 0, & N < 32 \end{cases} \tag{19}$$

$$\sigma = \frac{\mathrm{Median}(W_{1.k})}{0.6745} \tag{20}$$

Where.

- N Number of Wavelet coefficients
- $W_{1,k}$ Wavelet Coefficients on the particular scale
- j Scale of Wavelet decomposition
- σ Standard Deviation for noisy signals

A new shrinkage function

Objective

The basic concept of the wavelet shrinkage method is explained as: energy of a function is focused in the very few coefficients but the noise energy will spread all over the coefficients. Hence, Wavelet shrinkage functioni will focus on the coefficients which represent the function and make the other coefficients as zero. The major goal of this article is reducing the MSE value between original signal f and denoised signal $\hat{f}$.

Data vector can be assumed as follows:

$$y = [\,y_1, y_2, y_3, \ldots, y_M] \in \mathcal{R}^M \tag{21}$$

at equispaced locationx_M, then

$$y_i = f(x_i) + n_i \tag{22}$$

Here n – Standard Gaussian noise along independent identically distributed variable N(0,σ) & $f(x_i)$ are the samples of function f.

MSE of the given noisy function can be calculated:

$$R\left(\hat{f}, f\right) = \frac{1}{M}\sum_{i=0}^{M-1} E\left\{\hat{f} - f\right\}^2 \tag{23}$$

Modified minimax threshold function

It is very difficult to calculate an exact value of threshold in Wavelet based denoising method. A large threshold can shrink the maximum coefficients which make loss of information in the original signal and a small threshold will keep maximum coefficients in the signal which results a noisy signal. The selection of threshold value T is significant in the quality of denoising. Donoho and Johnstone suggested universal threshold concept and scale-dependent adaptive threshold concept [23] which provide best results when the function is not known.

In the universal thresholding, all the detailed coefficients are annihilated and minimax threshold will reduce the asymptotic risk. In order to overcome the shortcoming of the two methods above, an improved method based on them is proposed. The modified minimax thresholding can be expressed as:

$$T = \sigma\left(0.3936 + 0.10829\,\frac{\log N}{(N-1)}\right) \tag{24}$$

The standard deviation σ and mean μ of the vector can be defined as:

Table 1 Comparison of Wavelet Function based on SNR values (Noise Level is 50%)

Wavelet	Standard Minimax Function			Modified Minimax Function		
	Soft Shrinkage	Hard Shrinkage	K - Shrinkage	Soft Shrinkage	Hard Shrinkage	K - Shrinkage
Db4	31.4572	31.1841	32.2470	32.4591	31.7765	32.4653
Db8	31.4538	31.1794	32.5091	32.5323	31.7872	32.7178
Coif4	31.4491	31.1730	32.4914	32.5377	31.7614	32.7067
Sym4	31.4146	31.1498	32.0740	32.3464	31.7230	32.2940
Bior2.2	33.7763	33.3387	34.5468	34.5472	32.5048	34.6849

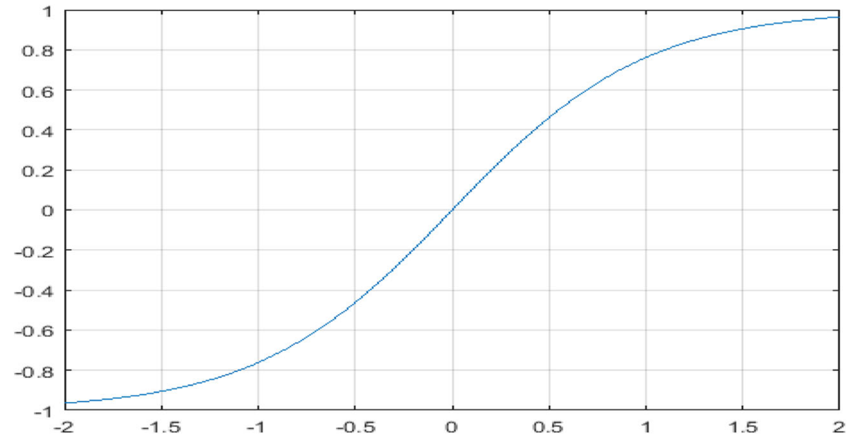

Fig. 1 Functional distribution of hyperbolic tangent function

$$\sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}|X_i-\mu|^2} \tag{25}$$

$$\mu = \frac{1}{N}\sum_{i=1}^{N}A_i \tag{26}$$

The modified minimax function will provide better SNR values compared to universal thresholding and minimax threshold. From Table 1, the SNR values of standard minimax thresholding and modified minimax thresholding are compared and it shows that a SNR value is improved.

K – Shrinkage function

The fundamental linear denoising model will perform as low pass filters which allow lower frequency in the channel and discard the remaining frequency which belong to higher frequency. The major issue in the linear denoising model is unsuitability because the noise present in the channel of low frequency are not removed but the application of biomedical signals remain low frequency.

The proposed K – Shrinkage function is also a nonlinear model and it is based on hyperbolic tangent function. The proposed function can outperform other shrinkage models. Hyperbolic function are called special function and it is expressed as a combination of exponential functions. The tangent hyperbola function can resemble the basic shrinkages among the family of Wavelet shrinkage function. The parameter β will resemble the tangent behavior such as hyperbolic function of the curve as shown in Fig. 1.

Pointwise distribution function of K – Shrinkage function are compared with the soft and hard shrinkage function as shown in Fig. 2 and the proposed function shows symmetry behavior. The exponential behavior of a function will maintain the significant empirical coefficient, which emphasis the signal characteristics and other empirical coefficients are shrink towards zero. Because of this, the number of coefficient required to represent the ECG signal characteristics will maintain and provide better MSE. The distribution properties of the K – Shrinkage model which also holds the symmetry property which is based on the soft shrinkage.

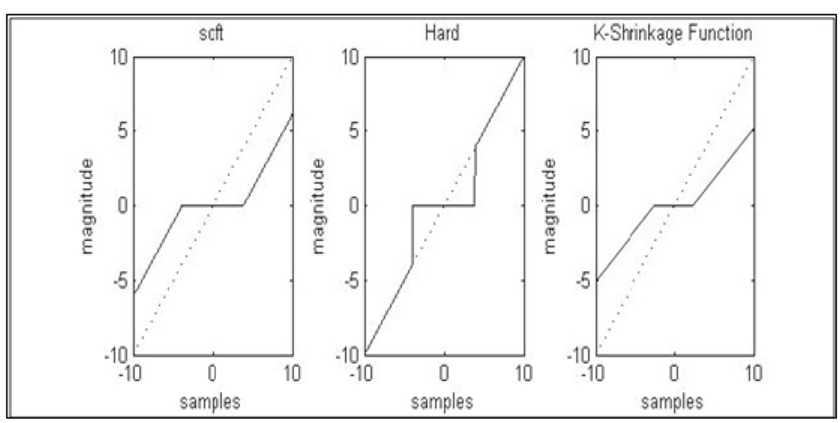

Fig. 2 Point wise distribution of various shrinkage functions

Table 2 Comparison of PRD values for the various Wavelet Function (Noise Level is 50%)

Wavelet	Standard Minimax Function			Modified Minimax Function		
	Soft Shrinkage	Hard Shrinkage	K - Shrinkage	Soft Shrinkage	Hard Shrinkage	K - Shrinkage
Db4	2.6739	2.7593	2.4415	2.3826	2.5742	2.3809
Db8	2.7632	2.7632	2.3689	2.3626	2.5742	2.3127
Coif4	2.6764	2.7628	2.3737	2.3611	2.5818	2.3156
Sym4	2.6870	2.7702	2.4906	2.4137	2.5933	2.4283
Bior2.2	2.0473	2.153	1.8735	1.8734	2.3701	1.8440

The K – Shrinkage model can be expresses as:

$$\delta_\lambda^k = \frac{I_0\left(\beta\sqrt{1-\left(\frac{2|x|}{N-1}-1\right)^2}\right)}{I_0(\beta)} \tag{27}$$

Where β is an adjustable parameter and $I_0(\beta)$ is the modified zero Bessel function of the first kind, given by

$$I_0(x) = 1 + \sum_{n=1}^{\infty}\left(\frac{(|x|/2)^2}{n!}\right) \tag{28}$$

Experimental results

Practical ECG signal consist of 2000 samples which has sampling rate of 360 Hz. It has been downloaded from the PhysioBank. The proposed method was simulated using MATLAB environment and tested with the different types of ECG signals. The normal and abnormal ECGs like right ventricular hypertrophy, acute myocarditis etc. are simulated for the robustness of proposed function. The other shrinkage function are failed to attain constant SNR value but K-Shrinkage has consistent.

The SNR [24, 25] can be expressed as

$$\mathrm{SNR(dB)} = 20\log\left[\frac{\mathrm{OriginalECG}}{\mathrm{OriginalECG}-\mathrm{NoisyECG}}\right] \tag{29}$$

In this paper, we use two threshold functions: Standard Minimax Function and Modified Minimax function. The different types of WT such as Daubechies Wavelet (DB4 and DB8), Coiflet Wavelet (COIF4), Symlet Wavelet (SYM4 and SYM8) and biorthogonal Wavelet (BIOR2.2) are simulated and the result were shown in Table 1. It is clear that the proposed threshold has shown on improvement for the noise level.

PRD [24, 25] is defined as

$$\mathrm{PRD} = \sqrt{\frac{\sum_{i=1}^{N}\left[x_{original}(i)-x_{recovered}(i)\right]^2}{\sum_{i=1}^{N}\left[x_{original}(i)\right]^2}} \times 100 \tag{30}$$

Where.

$x_{original}(i)$ i^{th} sample of the original signal
$x_{recovered}(i)$ i^{th} sample of the recovered signal

PRD is used to compare performance of the proposed function with other function for compression. The values of PRD for the different signals and WT have been shown in Table 2. It is observed that the low values have been achieved for larger Wavelets. The simulation has conducted for the various ECG signals from various sources and it has been observed that the Wavelet families of high order function are more suitable for compression of signal.

The proposed method has simulated using different types of Wavelet families and the results were shown in Table 3 for the different Wavelet families. It is clear that the simulation result show that the Daubechies Wavelet (DB4 and DB8) does not holds the symmetry property even if the SNR values have been improved. The COIF4 and SYM4 Wavelet hold near the symmetric property but the SNR values has been improved in the noise level of 20% to 50%; but it retains edge information of the source signal. From Table 3, it is clear that the BIOR2.2 Wavelet shows the SNR values has improved at the sustainable noise level but for the higher noise level it is decreased; however the reconstruction is better as illustrated in Fig. 3. The proposed K – Shrinkage function for the various Wavelet families are shown in Fig. 3 and it has been observed that the denoised ECG signal is more optimal for the visual representation using the BIOR2.2 Wavelet. BIOR2.2 wavelets are extremely suited for the analysis of ECG signal denoising because it is not energy preserving. The proposed K – Shrinkage function has the advantage of its signal ability at discontinuities over the soft shrinkage function which makes it unique among the shrinkage families.

Table 3 SNR based comparison of various ECG signals with different noise levels

ECG SIgnal	Noise Level	DB8			COIF4			SYM4			BIOR2.2		
		Soft Shrinkage	Hard Shrinkage	K - Shrinkage	Soft Shrinkage	Hard Shrinkage	K - Shrinkage	Soft Shrinkage	Hard Shrinkage	K - Shrinkage	Soft Shrinkage	Hard Shrinkage	K - Shrinkage
m100a	10	31.3234	31.076	31.8928	31.2596	31.1185	31.6398	31.287	31.0748	29.7945	34.6895	34.582	32.3408
	20	31.2929	31.0162	31.8605	31.2159	31.0382	31.599	31.2514	31.0302	29.8547	34.6128	34.4094	32.125
	30	31.2338	30.8341	31.814	31.1467	30.8369	31.5419	31.1859	30.8142	29.8815	34.4636	34.0121	31.8595
	40	31.129	30.5412	31.7538	31.0335	30.5303	31.4671	31.0669	30.508	29.8794	34.214	33.4206	31.5401
	50	30.9688	30.1499	31.6804	30.8643	30.143	31.3726	30.8911	30.121	29.8529	33.8644	32.7158	31.1623
m105a	10	32.9052	32.6725	33.01	27.6474	27.4351	33.0026	32.6595	32.6895	32.5328	35.9221	35.9814	35.2432
	20	32.8558	32.6188	32.9625	27.6314	27.4253	32.9545	32.6226	32.647	32.4971	35.8628	35.8669	35.2217
	30	32.7848	32.4794	32.8974	27.6094	27.3935	32.8886	32.5632	32.5247	32.445	35.7589	35.6043	35.1697
	40	32.6815	32.2032	32.8155	27.5795	27.3106	32.8057	32.4753	32.197	32.3771	35.5966	35.0224	35.0881
	50	32.5323	31.7872	32.7178	27.5376	27.1822	32.7067	32.3464	31.723	32.294	35.35	34.2932	34.9787
m203a	10	29.1349	28.6214	29.2649	29.1007	28.5845	29.2988	29.0142	28.5199	29.1949	31.5035	31.5592	35.2432
	20	29.1124	28.5782	29.2496	29.0779	28.5373	29.2822	28.9842	28.4432	29.1766	31.4823	31.541	35.2217
	30	29.0803	28.5111	29.2269	29.0463	28.4805	29.2581	28.9444	28.3639	29.1509	31.4522	31.4054	35.1697
	40	29.0358	28.4147	29.197	29.0047	28.3569	29.2267	28.8948	28.2587	29.1179	31.4016	31.2912	35.0881
	50	28.9793	28.2506	29.1601	28.949	28.206	29.1881	28.8343	28.1337	29.078	31.3306	31.0456	34.9787
m213b	10	26.3932	26.2094	26.5387	26.4269	26.2511	26.547	26.2762	26.217	26.2154	29.4472	29.5426	28.794
	20	26.3894	26.2021	26.535	26.4212	26.2449	26.5435	26.2743	26.1993	26.2159	29.4301	29.5199	28.7833
	30	26.3813	26.19	26.5263	26.4105	26.2292	26.5349	26.2673	26.187	26.2116	29.4043	29.4893	28.7643
	40	26.3674	26.1583	26.5128	26.3947	26.2173	26.5214	26.2564	26.1618	26.2027	29.369	29.4528	28.7371
	50	26.3482	26.1152	26.4944	26.374	26.1748	26.5029	26.2414	26.1261	26.1891	29.323	29.2831	28.7018

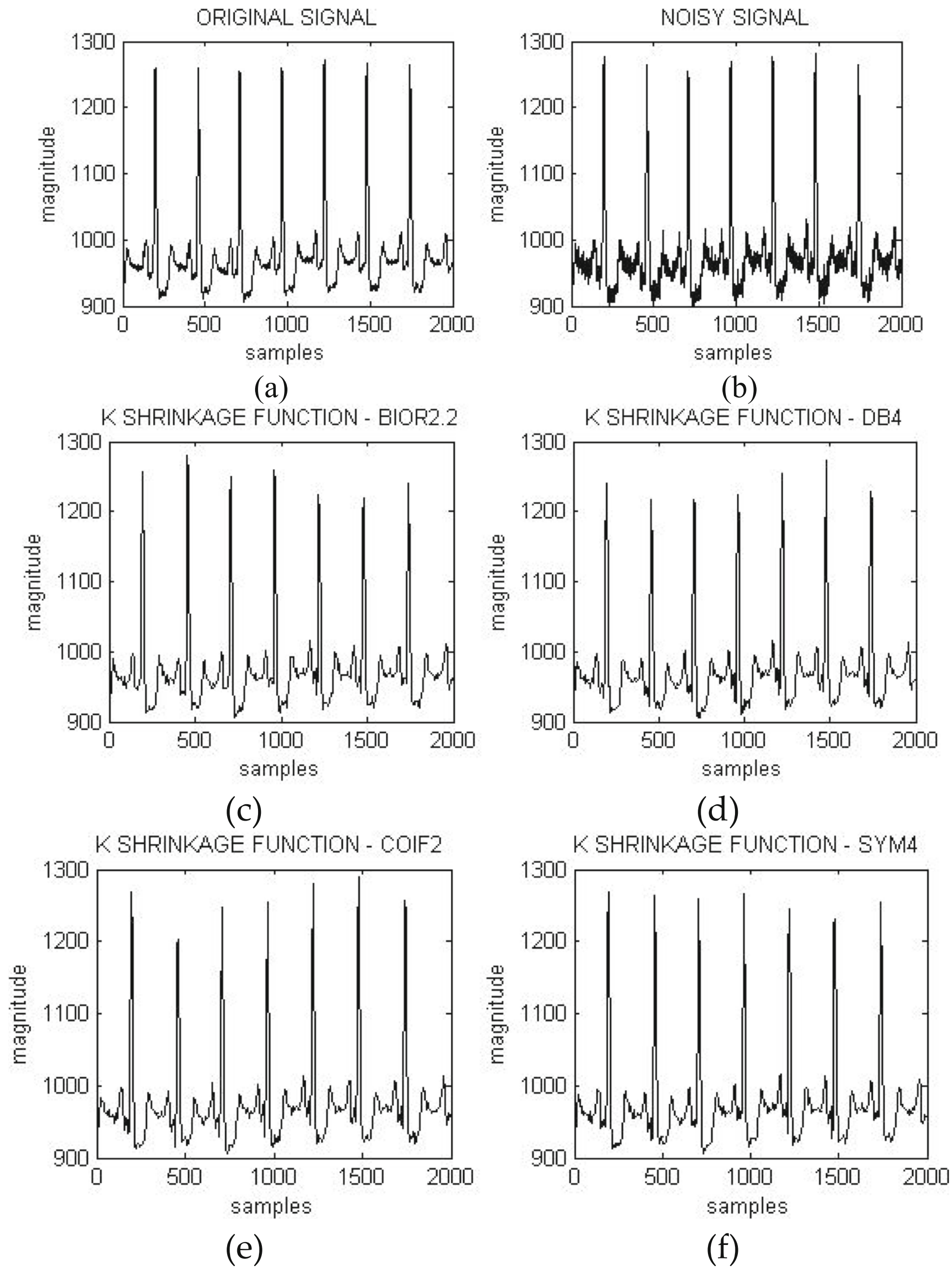

Fig. 3 **a** original signal (**b**) Noisy Signal (**c**) Biorthogonal Wavelets (**d**) DB4 Wavelets (**e**) COIF2 Wavelets (**f**) SYM4 Wavelets

Conclusion

There are wide range of Wavelet shrinkage models available for denoising the ECG signal. Each scheme illustrate the noise distributed in the signal and how to shrink it by removing the redundant Wavelet coefficients of every sub – band level. In this paper, we have introduced a novel K – Shrinkage model for denoising of ECG signal. This shrinkage function is simple and flexible since it provides the fine tuning of the shrinkage. The experiment was conducted using MATLAB for the various noises of the normal and abnormal ECGs. The result show that the above model has achieve good SNR in comparison to soft shrinkage. The proposed K – Shrinkage function has inherent in the application of denoising signals.

Compliance with ethical standards

Conflict of interest This paper has not communicated anywhere till this moment, now only it is communicated to your esteemed journal for the publication with the knowledge of all co-authors.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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