

## Review

# Noise and baseline wandering suppression of ECG signals by morphological filter

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Electrocardiogram (ECG) signals describe the electrical activity of the heart, and are universally used by physicians in the diagnosis of cardiac pathologies. However, during the acquisition of ECGs they are often contaminated with different sources of noise, making interpretation difficult. Different techniques have been used to filter the ECG signal, in order to optimize the signal to noise ratio (S/N). In this paper, an approach based on morphological filtering is developed in order to filter the ECG. Morphological filtering is concerned with the detection of the ECG morphology, therefore allowing the suppression of noises and particularly baseline wandering. The implemented filter is evaluated using signals taken from the MIT-BIH ECG universal database. The results show that the performance of this filter is good compared with other filtering techniques.

*Keywords:* ECG; Denoising; Baseline correction; Mathematical morphology; Morphological filtering

### 1. Introduction

Electrocardiogram (ECG) signals are often contaminated by various noises which can disturb the phase and amplitude characteristics of the signal [1–4]. The baseline corresponds to the layout which would be observed on an ECG if the heart did not have any electric activity. This line is generally horizontal if the patient does not carry out any movement [5–6], but during monitoring of the ECG signal, movements of the patient can modify the relative positions of the electrodes, which may lead to a corrugated layout of this line. Therefore good filtering is required.

Different methods have been developed to filter baseline wandering and noise, including band-pass filtering, which reduces the influence of muscle noise, 60 Hz interference and baseline wandering [7]. A band-pass filter was constructed from a low-pass filter and cascaded high-pass filter. A second technique is the adaptive filter [8]. This is based on the least mean square method, to minimize the mean

square error between the primary input and the reference input. The structure of the combined linear adaptive filter is transformed to a simple and effective linear comb filter. Thirdly, the wavelet denoising technique was also used [9]. This was based on generating a constructed denoised ECG signal by extracting and combining the delimited QRS complexes from the second-level wavelet denoising, and the P and T waves from the fourth- or fifth-level wavelet denoising outputs. The most suitable wavelet function and decomposition discrete wavelet transform (DWT) level for the denoising process are determined by means of the mean square error value. Each author claims good results when ECG signals from the MIT-BIH database were tested [7–9].

In this work we are interested in morphological filtering. The filter is implemented under the MATLAB 7 environment and evaluated using ECG signals from the MIT-BIH universal database [10]. Morphological filtering is widespread in the field of signal processing and image processing, due to its robustness and simple and fast

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calculation [11–13]. In this article we propose a modified version of morphological filtering—modified morphological filtering (MMF)—for the correction of the baseline and the suppression of noise in ECG signals [14].

Morphological filters are nonlinear signal transformations that locally modify geometric feature signals, and also satisfy causality [15]. They stem from the basic operation of a set-theoretical method for signal analysis—mathematical morphology of opening and closing [16]. These operators constitute a fundamental stage of morphological filter, and are modified to become modified morphological filtering.

The paper is organized as follows. The mathematical morphology (MM) operator is introduced in §2. The MMF algorithm for the ECG signal is described in §3. The experimental results are presented and discussed in §4 and evaluated in §5. Finally, a conclusion is given in §6.

## 2. Mathematical morphology

Mathematical Morphology is a branch of mathematics which present strong bonds with the algebra and trellis theory and probability [17–18]. The development of mathematical morphology was inspired by problems in signal processing, which is its principal field of application.

One of the basic ideas of mathematical morphology is to study or treat a set with the help of another set, called the structuring element, which is used as a probe [19]. Each position of the structuring element is assessed as if it touches or is included as an initial set. According to the answer, a set of outputs is built, to obtain basic operators to obtain basic operators which are explained in the next title 2. Such morphological operators privilege the concept of form than information on the amplitude of the signals, when these are used in signal processing. Mathematical morphology is a nonlinear method of signal processing based on two morphological operators (erosion and dilation) and two others which combine the first two (opening and closing). These morphological operators use a form of reference, called the structuring element, with which the signal or image is compared locally. The following paragraphs explain this concept in more detail.

### 2.1. Basic morphology operators

Mathematical morphology has been introduced in principle as a signal processing method, based on set theory [20–21]. The basic concept of mathematical morphology is to modify the shape information of a signal, considered a set, by transforming it through its interaction with another object, called the structuring element. In practice, the structuring element is compact and of a simpler shape than the original object.

**2.1.1. Morphological processing of sets.** Morphological filters of sets are set processing filters processing input  $m$

–  $D$  sets by interacting them via Minkowski set addition or subtraction with structuring elements that are compact  $n - D$  sets ( $n \leq m$ ). For this purpose two basic operations are introduced by mathematical morphology. The first one derives from the following. If  $A \subseteq R^m$  and  $B \subseteq R^m$  the set  $A \oplus B$  is defined as:

$$A \oplus B = \{a + b : a \in A, b \in B\} = \bigcup_{a \in A} B_a = \bigcup_{b \in B} A_b, \quad (1)$$

where  $A_b = \{a + b : a \in A\}$  is a set obtained by shifting the origin of the set  $A$  at distances determined by the element  $b$  of the set  $B$ ;  $\in$  denotes the set inclusion, and  $\cup$  denotes the set union. This operation is called the Minkowski addition. The second operation was introduced by Hadwiger under the name of Minkowski subtraction. It associates to  $A$  and  $B$  the set  $A \ominus B$ , defined by:

$$A \ominus B = \{A^C \oplus B\}^C = \bigcap_{b \in B} A_b, \quad (2)$$

where  $A^C$  denotes the complement of the set  $A$ ,  $\cap$  denotes the set intersection and  $A_b$  is a set obtained by shifting the origin of the set  $A$  at distances determined by the elements of the set  $B$ . Let  $B^S = \{-b : b \in B\}$  denote the symmetric set of  $B$  with respect to the origin, and  $\emptyset$  denote the empty set.

The basic morphological processing of sets are the erosion  $A \ominus B^S$ , dilation  $A \oplus B^S$ , opening  $A \circ B$ , and closing  $A \bullet B$  of  $A$  by  $B$ . These operations are defined as follows:

$$A \ominus B^S = \{x : B_x \subseteq A\} = \bigcap_{b \in B} A_{-b} \quad (3)$$

$$A \oplus B^S = \{x : B_x \cap A \neq \emptyset\} = \bigcup_{b \in B} A_{-b} \quad (4)$$

$$A \circ B^S = (A \ominus B^S) \oplus B \quad (5)$$

$$A \bullet B^S = (A \oplus B^S) \ominus B. \quad (6)$$

From equations (3)–(6) and figure 1 we observe the following. Geometrically, the erosion of  $A$  and  $B$  are defined as the set of all point  $x$  such that the moving  $B_x$  is contained in the original set  $A$ ; the dilation of  $A$  by  $B$  is defined as the set of all point  $x$  such that  $B_x$  intersects  $A$ . Algebraically, the erosion of  $A$  by  $B$  is equal to the Minkowski set subtraction of  $B^S$  from  $A$ ; the dilation of  $A$  by  $B$  is the Minkowski sum of  $A$  and  $B^S$ . Dilating  $A$  is equivalent to eroding  $A^C$  and complementing the result as implied by equation (2). The opening of  $A$  by  $B$  is the set resulting from erosion of  $A$  by  $B$  followed by the Minkowski sum with  $B$ ; this cascade does not generally recover  $A$ , but rather a subset of  $A$  which is the morphologically most essential part with respect to  $B$ . From equations (1), (3) and (5) it follows that:

$$A_B = \bigcup_{B_x \subseteq X} B_x. \quad (7)$$

An example of closing and opening operations is further shown in figure 1. An interesting consequence of the properties listed in table 1 is that the set resulting from the closing operation always includes the initial set. Figure 1 shows that erosion shrinks the set  $A$ , whereas dilation expands  $A$ .

The opening suppresses the sharp capes and cuts the narrow isthmuses of  $A$ , whereas the closing fills in the thin gulfs and small lobes. Thus, if the structuring element  $B$  has a regular shape, both opening and closing can be thought of as nonlinear filters which smooth the contours of the input signal.

The dual operation of opening is the closing operation. Morphological closing of the set  $A$  by the set  $B$  can be expressed as a dilation operation followed by erosion of the dilated result, using the same structuring element. Some basic properties of erosion and dilation are summarized in table 2 and basic properties of closing and opening are defined in table 1.

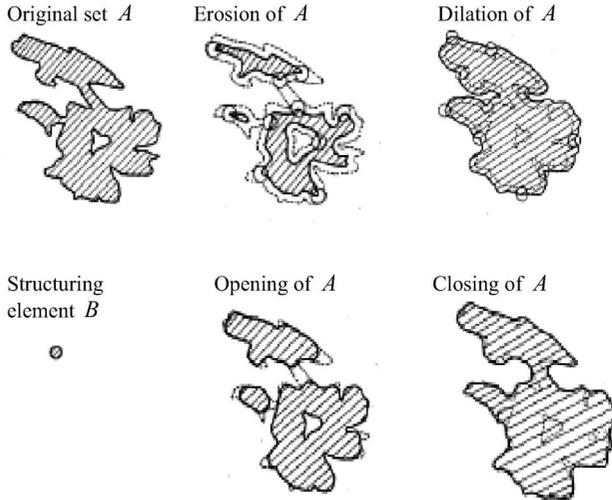


Figure 1. Erosion, dilation, opening and closing of a set  $A$  (original set) by  $B$ . The shaded areas correspond to the interior of the set, the dark solid curve to the boundary of the transformed sets, and the dashed curve the boundary of the original set.

Table 1. Basic properties of closing and opening.

Closing	Opening
Extensivity: $A \subseteq A \bullet B$	Antiextensivity: $A \circ B \subseteq A$
Idempotence: $(A \bullet B) \bullet B = A \bullet B$	Idempotence: $(A \circ B) \circ B = A \circ B$
Translation invariance: $(A)_x \bullet B = (A \bullet B)_x$	Translation invariance: $(A)_x \circ B = (A \circ B)_x$
Increasing: $A_1 \subseteq A_2 \Rightarrow A_1 \bullet B \subseteq (A_2 \bullet B)$	Increasing: $A_1 \subseteq A_2 \Rightarrow A_1 \circ B \subseteq (A_2 \circ B)$
Duality: $(A \bullet B)^C = A \circ B$	Duality: $(A \circ B)^C = A \bullet B$

**2.1.2. Morphological processing of signals.** The basic concept of morphological signal processing is to modify the shape of a signal, by transforming it through its intersection with another object called the structuring element. The shape information of a signal can be extracted by using a structuring element to operate on the signal. Thus, a structuring element has to be designed depending on the shape characteristics of the signal that is to be extracted.

There are two possible cases in functional mathematical morphology. The structuring element can be:

- flat; or
- voluminal; e.g. affected by grey-level amplitude in images.

We are interested here with the structuring case of a flat element. For the same reasons, all these transformations will be illustrated in only one dimension on the ECG signal.

The basic operators of modified morphological filtering include dilation ( $\oplus$ ), erosion ( $\ominus$ ), opening ( $\circ$ ) and closing ( $\bullet$ ) [22–23].

Let  $f(n)$  be the original 1D signal, which is the discrete function over a domain  $f(n) = \{0, 1, \dots, N-1\}$ . And let  $B(m)$  be the structuring element, which is the discrete function over a domain  $B(m) = \{0, 1, \dots, M-1\}$ . Two basic morphological operators, the erosion and the dilation, can be defined as:

$$(f \ominus B)(n) = \underset{m=0, \dots, M-1}{\text{MIN}} \{f(n+m) - B(m)\} \quad (8)$$

$$(f \oplus B)(n) = \underset{m=0, \dots, M-1}{\text{MAX}} \{f(n-m) + B(m)\}, \quad (9)$$

where  $\ominus$  denotes the operators of erosion and  $\oplus$  denotes the operators of dilation. Based on the dilation and erosion, two other basic morphological operators, opening ( $\circ$ ) and closing ( $\bullet$ ) can be further defined:

$$(f \circ B)(n) = (f \ominus B \oplus B)(n) \quad (10)$$

$$(f \bullet B)(n) = (f \oplus B \ominus B)(n). \quad (11)$$

Table 2. Basic properties of dilation and erosion.

Dilation	Erosion
Commutative: $A \oplus B^S = B^S \oplus A$	Non-commutative: $A \ominus B^S \neq B^S \ominus A$
Associative: $(A \oplus B^S) \oplus C^S$ $= A \oplus (B^S \oplus C^S)$	Translation invariance: $(A)_x \ominus B^S = (A \ominus B^S)_x$
Translation invariance: $(A)_x \oplus B^S = (A \oplus B^S)_x$	Increasing: $A_1 \subseteq A_2 \Rightarrow A_1 \ominus B^S \subseteq A_2 \ominus B^S$
Increasing: $A_1 \subseteq A_2$ $\Rightarrow A_1 \oplus B^S \subseteq A_2 \oplus B^S$	Decreasing: $B_1 \subseteq B_2$ $\Rightarrow A_1 \ominus (B_2)^S \subseteq A_1 \ominus (B_1)^S$
Duality: $A \oplus B^S = (A^C \ominus B)^C$	Duality: $(A \ominus B^S)^C = A^C \oplus B$

To obtain the eroded function of  $f(n)$ , we attribute to  $f(n)$  its minimal value in the field of the structuring element  $B(m) = (0,0,0,0,0)$  which is a line segment, and with each new displacement of  $B(m)$ , the structuring element  $B(m)$  plays the same role as a moving window. The width of such window is chosen empirically as  $B = 5$ . This is illustrated in figure 2, where these operations are applied to an ECG signal. The illustration shows a reduction in the peaks of the ECG signal and a widening of the valleys. Erosion is an operator of shrinking in which the values of  $f \ominus B$  are always less than those of  $f$ .

Similarly, the dilation can be performed by taking of set sums. Its complexity is the same as erosion and is related to convolution, where instead of doing summation of products, a maximum of sums is computed. This transformation fills the valleys and thickens the peaks. Figure 2 shows that dilation is an operation of expansion in which values of  $f \oplus B$  are always greater than those of  $f$ .

Morphological opening can be expressed as an erosion operation followed by a dilation of the eroded result, using the same structuring element. The dual operation of opening is the closing operation. Morphological closing can be expressed as a dilation operation followed by an erosion of the dilated result, using the same structuring element.

Figure 2 shows that the opening by  $B$  smooths the graph off from below by cutting down its peaks. The closing smooths the graph of  $f$  from above by filling up its valleys (suppress pits).

Subtracting from  $f$  its opening or closing by  $B$  provides respectively the peaks and valleys of  $f$ . The width of these peaks and valleys depends on the size of  $B$ . Therefore, opening and closing by a structuring element  $B$  can be used effectively to suppress noise and for baseline wandering detection in ECG signals.

In practice, the morphological operators that are chosen are based on different application scenarios of signal processing. Sometimes it is difficult to obtain prior knowledge of the noise impulse from a signal, especially when it has both positive and negative impulses of noise. If this is the case, some combinations of the four operators need to be defined, such as the average (AVG) filter formulated below:

$$AVG(f) = (f \bullet B + f \circ B) / 2 \quad (12)$$

The average filter can be used to flatten the noise impulse, corresponding to the smoothing filter. The difference filter (DIF) can be used to extract the impulsive features, namely:

$$f \bullet B - f \circ B = (f \bullet B - f) + (f - f \circ B) \quad (13)$$

$f \bullet B - f$  and  $f - f \circ B$  are two types of morphological top-hat transform [24, a high-pass filter with good performance.  $f \bullet B - f$  is called the black top-hat transform, and is used to extract negative impulse of noise;  $f \circ B - f$  is called the

white top-hat transform, and is used to extract positive impulse of noise. Thus the filter can be used to extract all noises impulses simultaneously.

### 3. Modified morphological filtering algorithm for the ECG signal

In the MMF algorithm [25], the baseline correction and noise suppression are performed as follows:

$$f_b = f_o \circ B_o \bullet B_c \quad (14)$$

$$\begin{aligned} f &= \frac{1}{2} ((f_o - f_b) \bullet B_{pair} + (f_o - f_b) \circ B_{pair}) \\ &= \frac{1}{2} (f_{bc} \oplus B_1 \ominus B_2 + f_{bc} \ominus B_1 \oplus B_2) \end{aligned} \quad (15)$$

Figure 3 is a block diagram describing the structure of the MMF of the ECG signals. It consists of five blocks. The first is concerned with the acquisition of ECG signals ( $f_o$ : original ECG signal). This step is followed by another which allows the detection of the baseline drift. This detection is achieved using the morphological operators defined in equation (14).  $B_o$  and  $B_c$  are structuring elements for opening and closing. This baseline drift is subtracted from the original ECG signal leading to a correction of baseline  $f_{bc}$ .

The following steps aim to exploit this correction of baseline to remove the noise and finally to generate a filtered ECG signal  $f$ , which is the resulting signal after noise suppression. It is achieved through the suppressing approach given above (15).  $B_{pair}(B_1, B_2)$  is selected according to the purpose of analysis and the morphological properties of the ECG signal.  $B_1$  is selected to be a triangular shape to retain the peaks and valleys and  $B_2$  is a line segment to remove noise. Therefore, the shape, length and height (amplitude) of structuring element should be selected according to the signal to be analysed. The shape of structuring element can vary from regular to irregular curves, such as flat, triangle and semicircle.

### 4. Results and interpretation

The MMF is implemented and tested using ECG signals from the MIT-BIH database. The ECG signals selected for these tests have high level of noise and baseline wandering. As can be seen from figures 4 and 5, which illustrate a noisy ECG signal (record 101) and ECG signals after baseline correction (figure 4) and the resulting filtered ECG signal (figure 5), the algorithm operates as follows.

First, the ECG signal is opened by a structuring element  $B_o$ , which means two morphology operations are applied: erosion and dilation. The first removes the peaks and enlarges the width of minimum regions, and the second increases dilation, preserves the valleys and enlarges the width of maximum regions.

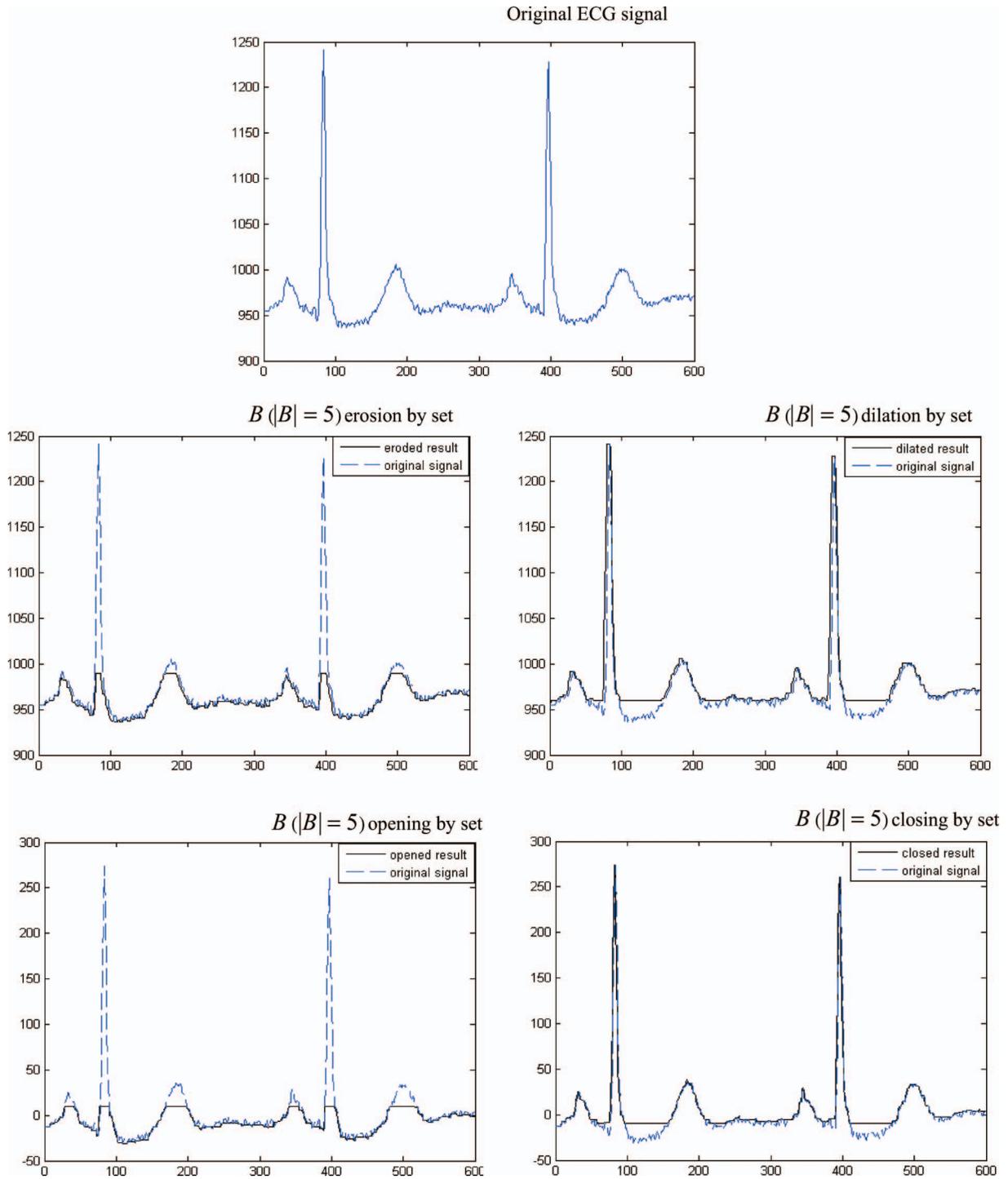


Figure 2. Erosion, dilation, opening and closing of signal by a set  $B = (0,0,0,0,0)$ .

The operation of opening by the structuring element  $B_o$  generates a signal made up of valleys which are removed by the second operation, i.e. closing dilation + erosion, by the structuring element  $B_c$ . This leads to the baseline drift  $f_b$ , which is illustrated in figures 4(b)–4(c). After selecting the morphological operators, the structuring element  $B(B_o, B_c)$  is the next key component which is

used for correction of the baseline in the morphology analysis. Generally, only when the shape information of the ECG signal is matched to those of structuring element can the ECG signal be preserved. Therefore, the shape, length and height of the structuring element should be selected according to the ECG signal to be extracted, i.e. the baseline drift.

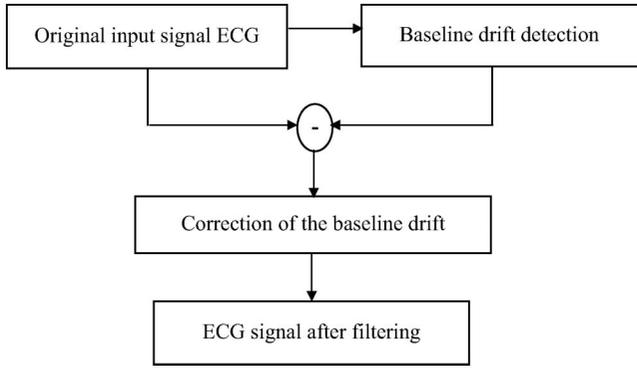


Figure 3. Block diagram of MMF.

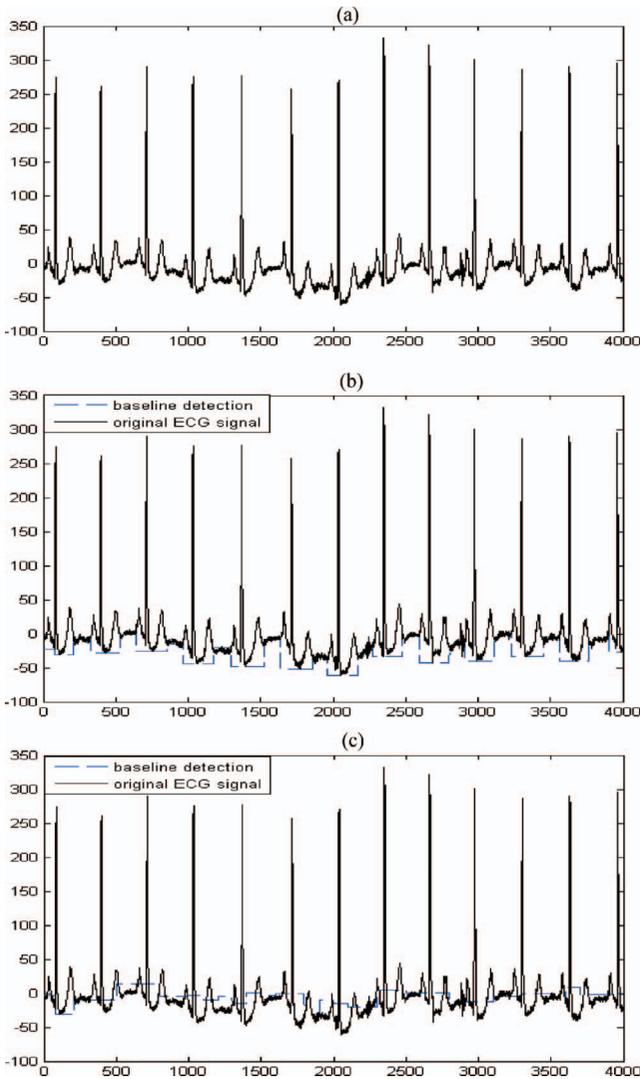


Figure 4. Results of baseline detection by MMF: (a) original ECG signal 101; (b) baseline detection with a varying minimum; (c) baseline detection, with a fixed minimum.

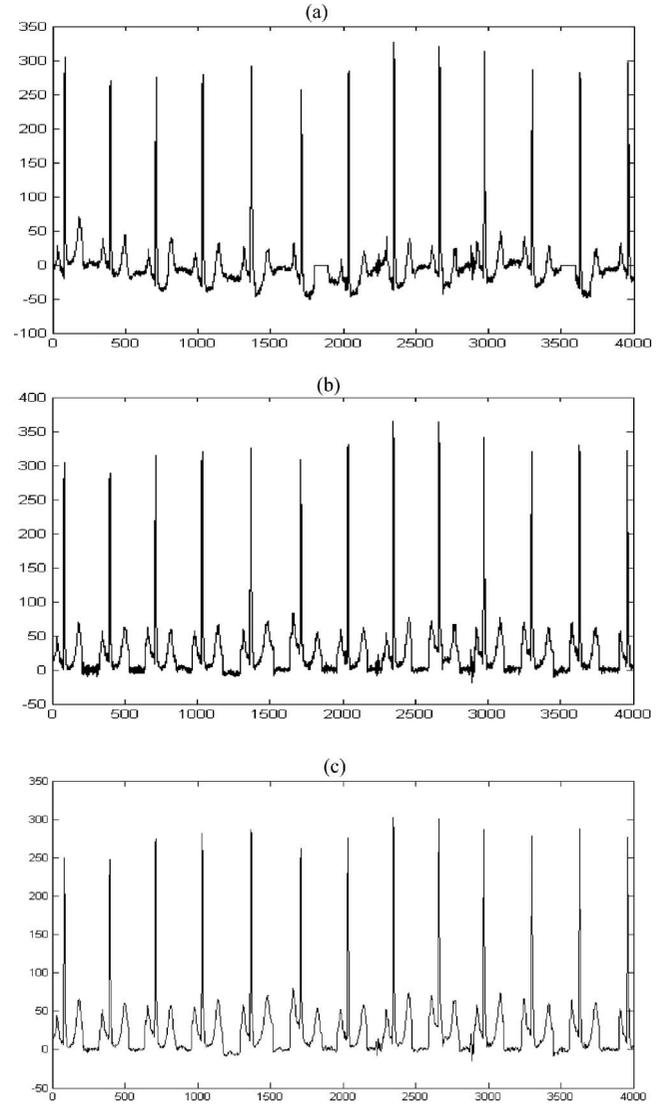


Figure 5. Results of the baseline correction and denoised signal by MMF: (a) baseline correction with a fixed minimum; (b) baseline correction with a varying minimum; (c) denoised signal with a varying minimum.

In our algorithm, flat structuring elements  $B(B_o, B_c)$  are used for correction of the baseline. They were selected because they present the simplest structuring element with a straightforward application. Thus,  $B_c$  and  $B_o$  took different lengths and it depends on the duration (or width) of the characteristic wave and the sample frequency ( $F_S = 360$  Hz) of the ECG signal.

The ECG signal consists of the QRS complexes, P and T waves. Their duration  $D_w$  is generally up to 0.2 s, therefore leading to a number of  $D_w F_S$  samples during this element. So the structuring element  $B_o$  is selected as  $L_o = 0.2 F_S$  to be of length larger than  $D_w F_S$ , to extract the wave characteristic. The length of the structuring element  $B_c$  is selected to be longer than  $B_o$ , at about  $1.5 L_o$ , because the closing

operation is used to remove the valleys left by the opening operation.

The results we obtained show that the minimum, i.e. erosion in the operation of closing, plays a very significant role for the detection of the baseline drift. Figure 4(c) illustrates the case where the minimum is selected with a fixed value  $[-3, 4]$ . To improve this result the minimum must be selected proportional to the variation of the baseline drift.

This correlation of the variation of the minimum with the baseline is illustrated in the operation of closing  $\max + \min$ , such as the maximum is fixed at a value correlated to the variations of the baseline (figure 4(b)). The final stage leading to the correction of the baseline is the subtraction of disturbed ECG signal with the detected baseline drift signal  $f_b$ .

Figure 5(a) illustrates the case where baseline correction is achieved respectively by a fixed minimum value and varying the minimum value; and the denoised ECG signal. Similarly, figures 6(b), 7(b) and 8(b) illustrate the case where the minimum of the operation of closing is selected to be proportional to the variation of the baseline drift applied to the ECG signal with more baseline drifts and noise. The following steps of the algorithm are as follows.

After the correction of the baseline drift, the following stage is the suppression of noise. This consists of the application of operators of modified morphologies. In fact, the signal obtained after correction of the baseline is treated simultaneously by the closing and opening operations, followed by a summation then a division by two, to generate at the end the filtered signal. Thus, the AVG filter can be used to delete the noises impulses.

It should be noted that the shape of the structuring element in the suppression of noise is different to that from the correction of the baseline. Indeed, it can take two different forms of equal lengths: a triangular form  $B_1$  to maintain the peaks and the valleys, or a straight form (segment of null amplitude)  $B_2$ . In our case the size of the structuring element was fixed at five sample units each, with values of  $B_1 = (0,1,5,1,0)$  and  $B_2 = (0,0,0,0,0)$ . This value is fixed in an empirical way where the minimum and the maximum are fixed at optimal values in the stage of the suppression of the noise. As shown in figures 6(c) and 8(c), good suppression of the noise can be observed.

## 5. Evaluation of results

In this section we will compare two methods, morphological filtering and denoising by thresholding wavelet shrinkage [26]. Denoising by the thresholding wavelet shrinkage method is based on the following points:

- The characteristics of a signal can be represented by a reduced number of coefficients.

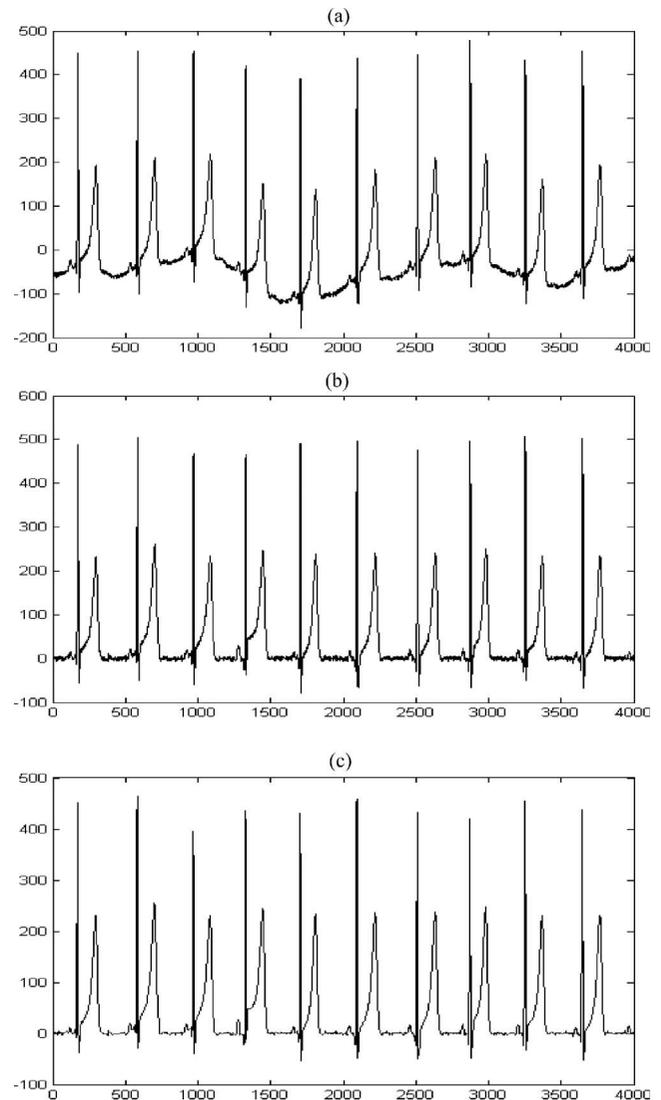


Figure 6. Results of MMF: (a) original ECG signal 113; (b) signal after baseline correction; (c) denoised signal.

- The noise affects all wavelet coefficients.
- By reducing wavelet coefficients to zero, the noise can be removed by preserving the characteristics of the signal.
- The use of thresholding methods makes it possible to determine the value of the threshold starting from the statistics of the signal.

We saw that it was possible to carry out a decomposition in wavelets of a signal, then to rebuild this signal starting from its wavelet coefficients. However, this technique would not have been of great interest if these coefficients were not modified, because one would obtain a final signal identical to the initial signal. Therefore, to filter a signal by thresholding, one should follow the stages represented by the diagram in figure 9.

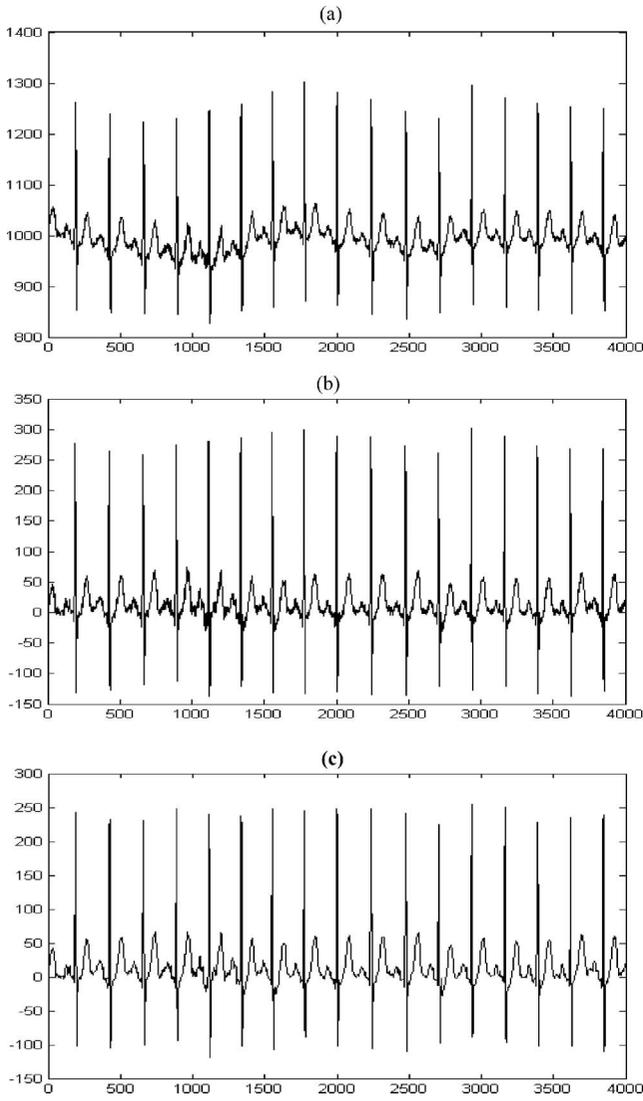


Figure 7. Results of MMF: (a) original ECG signal 209; (b) signal after baseline correction; (c) denoised signal.

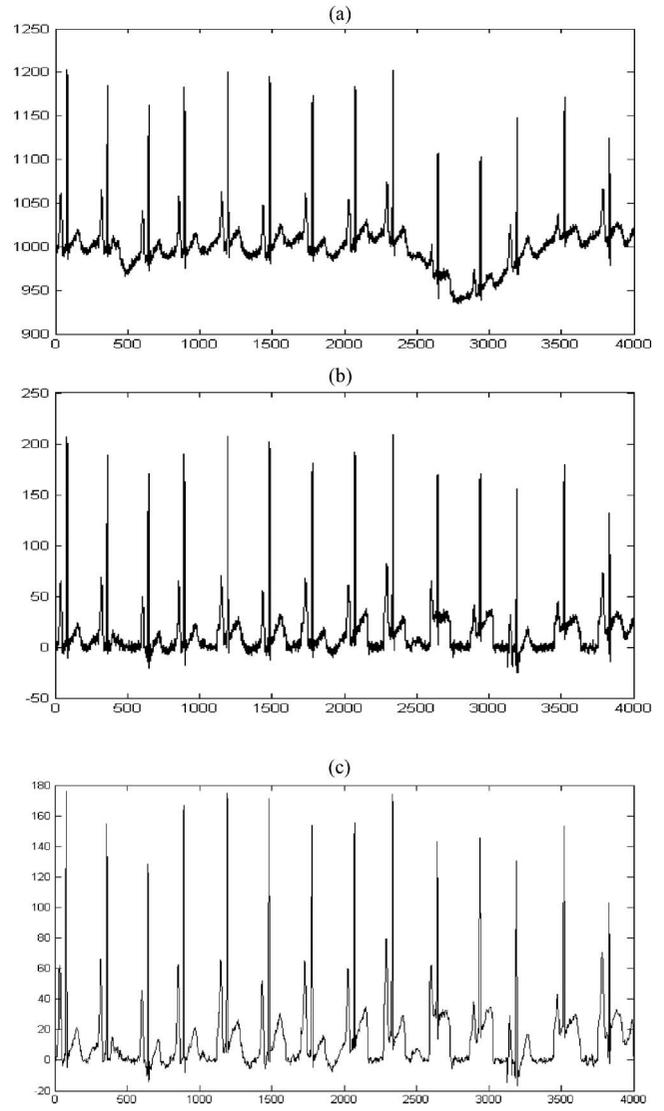


Figure 8. Results of MMF: (a) original ECG signal 222; (b) signal after baseline correction; (c) denoised signal.

### 5.1. Filtering evaluation criteria

So far we have evaluated the filtering performance using only qualitative criteria. A quantitative evaluation is also required to have an overall assessment of filtering. The parameters used are signal to noise ratio (SNR), root mean square error (RMSE), mean squared error (MSE) and normalized mean squared error ( $MSE_n$ ). These are given by:

$$SNR = 10 \log \frac{\sum_{n=1}^N (f(n) - \bar{f})^2}{\sum_{n=1}^N (f(n) - \tilde{f})^2} \quad (16)$$

$$RMS = \sqrt{\frac{\sum_{n=1}^N (f(n) - \tilde{f}(n))^2}{N}} \times 100 \quad (17)$$

$$MSE = \frac{\sum_{n=1}^N (f(n) - \tilde{f}(n))^2}{N} \times 100 \quad (18)$$

$$MSE_n = \frac{\sum_{n=1}^N (f(n) - \tilde{f}(n))^2}{\sum_{n=1}^N (f(n))^2} \times 100 \quad (19)$$

The correlation is calculated between the noising signal and the filtering signal. In the above equations  $\tilde{f}$  = rebuilt signal;  $\bar{f}$  = the average of the original signal; and  $f$  = original signal. Tables 3–5 represent the results obtained for each method. It can be clearly seen that the morphological filtering results are better than the wavelet results; the SNR value and the correlation in morphological

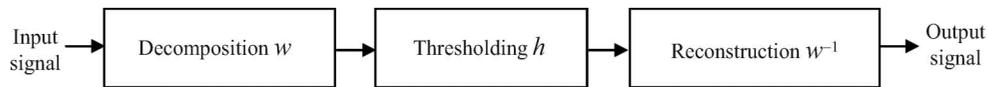


Figure 9. Block diagram of the wavelet.

Table 3. Criteria for evaluating the filtering of signal 101.

	Morphological filter	Wavelet
SNR	28.66	27.92
RMS	1.50	2.10
MSE	3.01	4.12
MSE <sub>n</sub>	0.0014	0.0150
Correlation	0.9997	0.9980

Table 4. Criteria for evaluating the filtering of signal 113.

	Morphological filter	Wavelet
SNR	35.44	35.10
RMS	1.14	1.33
MSE	2.12	1.99
MSE <sub>n</sub>	0.0001	0.0022
Correlation	0.9999	0.9990

Table 5. Criteria for evaluating the filtering of signal 209.

	Morphological filter	Wavelet
SNR	18.14	17.99
RMS	1.45	1.99
MSE	1.66	2.05
MSE <sub>n</sub>	0.0012	0.0045
Correlation	0.9881	0.7990

filtering are larger than the wavelet values. However we found that the RMSE, MSE and MSE<sub>n</sub> values in morphological filtering were too weak in comparison to the wavelet values.

## 6. Conclusion

In this work we implemented a modified version of morphological filtering. It was shown that using morphology operators, closing and opening a filtering operation can be implemented. This implementation was tested and evaluated for suppression of baseline drift and noise in ECG signals. The results illustrate the good performance of such an approach and show that the choice of the minima of the operations of closing is important, as it can affect detection of the variations of baseline drift, and consequently performance of the filter.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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