Wavelets, Statistics, and Biomedical Applications

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SUMMARY

This paper emphasizes the statistical properties of the wavelet transform (WT) and discusses some recent examples of applications in medicine and biology.

The redundant forms of the transform (continuous wavelet transform (CWT) and wavelet frames) are well suited for detection tasks (e.g., spikes in EEG, or microcalcifications in mammograms). The CWT, in particular, can be interpreted as a prewhitening multi-scale matched filter. Redundant wavelet decompositions are also very useful for the characterization of singularities, as well as for the time-frequency analysis of non-stationary signals. We briefly discuss some examples of applications in phonocardiography, electrocardiography (ECG), and electroencephalography (EEG).

Wavelet bases (WB) provide a similar, non-redundant decomposition of a signal in terms of the shifts and dilations of a wavelet (hierarchical or pyramidal transform). There are also non-hierarchical versions that constitute a direct extension of the traditional block transforms (Fourier, DCT, etc..). This makes WB well suited for any of the tasks for which block transforms have been used traditionally: data compression, data analysis (decorrelation), and data processing (generalized filtering). Wavelets, however, may present certain advantages because they can improve the signal-to-noise ratio, while retaining a certain degree of localization in the time (or space) domain. We present three illustrative examples. The first is a straightforward denoising technique that applies a soft threshold in the wavelet domain. The second is a more refined version that uses generalized Wiener filtering; it was initially proposed for reducing noise in evoked response potentials. The third is a statistical method for detecting and locating patterns of brain activity in functional images acquired using magnetic resonance imaging (fMRI).

Finally, we conclude by describing a wavelet generalization of the classical Karhunen-Loeve transform. In particular, we provide the solution for the optimal decomposition of a wide sense stationary process (unconstrained case).

1. THREE TYPES OF WAVELET TRANSFORMS

The wavelet transform is a linear signal transformation that uses templates $\psi_{(a,b)} = a^{-1/2}\psi((x-b)/a)$, which are shifted (index b) and dilated versions (index a) of a given wavelet function $\psi(x)$ [11, 53]. The wavelet transform of the signal $f \in H$ is parameterized by the scale and shift parameters a and b; it is typically written as

$$T_\psi f(a,b) = \langle f, \psi_{(a,b)} \rangle, \tag{1}$$

where $\langle \cdot,\cdot \rangle$ is the inner product associated with the Hilbert space H (l_2 or L_2 depending on whether the signal f is discrete or continuous). A basic requirement is that the transform is reversible, that is, that the signal f can be reconstructed from its wavelet coefficients $T_\psi f(a,b)$. The distinction between the various types of wavelet transforms depends on the way in which the scale and shift parameters are discretized.

At the most redundant end, one has the continuous wavelet transform (CWT) for which these parameters vary in a continuous fashion [20]. This representation offers the maximum freedom in the choice of the analysis wavelet. The only requirement is that the wavelet satisfies an admissibility condition; in particular, it must have zero mean.

In practice, it is often more convenient to consider the WT for some discretized values of a and b (e.g., the dyadic scales $a = 2^i$ and integer shifts $b = k$ with $(i,k) \in Z^2$). The transform will be reversible if and only if the corresponding (countable) set of templates defines a wavelet frame (WF) [10, 19, 1]. In other words, the wavelet must be designed such that

$$\forall f \in H, \quad A \cdot \|f\|^2 \le \sum_{a,b} \left|\langle f, \psi_{(a,b)} \rangle\right|^2 \le B \cdot \|f\|^2 \tag{2}$$

where A and B are two positive constants (framebounds).

A WF is just a redundant version of a wavelet basis (WB) which can be obtained for the critical sampling rate: $a = 2^i$, $b = 2^i \cdot k$ with $(i,k) \in Z^2$. In this case, the templates must also be linearly independent, which imposes even stronger constraints on the choice of ψ. If the framebounds in (2) are such that $A = B = 1$, then the transformation is orthogonal. Such wavelets can be constructed by starting from a multiresolution analysis of L_2 [26, 27]. The better known examples are the Daubechies wavelets [9], which are orthogonal and compactly supported; and the Battle-Lemarié wavelets which are splines with exponential decay [24, 27]. In the case of semi- and bi-orthogonal wavelet bases [8, 49, 2], one has the following signal representation

$$f = \sum_i \sum_{k \in Z} \langle f, \tilde{\psi}_{i,k} \rangle \cdot \psi_{i,k} \quad , \tag{3}$$

with the short form convention $\psi_{i,k} = 2^{-i/2}\psi(x/2^i - k)$. The analysis wavelet $\tilde{\psi}$ is the dual of ψ (the synthesis wavelet); in the orthogonal case, both wavelets are identical.

Basic texbook references on the wavelet transform are [11, 29, 53]. For computational issues, we refer the reader to [46]. An extensive review of its various uses in medicine and biology is given in [47]; specific biomedical applications are also described in [3].

2. WAVELET ANALYSIS AND FEATURE DETECTION

The redundant forms of the transform (CWT and WF) are usually preferable for signal analyses, feature extraction, and detection tasks for they provides a description that is truly shift-invariant. Next, we discuss some wavelet properties that are of special interest for this class of applications.

A. Wavelets and time-frequency analysis

An analysis wavelet ψ is typically a well localized bandpass function with a central frequency at ω_0; a standard requirement is that its time-frequency bandwitdth product is close to the limit specified by the uncertainty principle: $\Delta_\psi \cdot \Delta_{\hat{\psi}} \geq 1/2$. Thus, each analysis template $\psi_{(a,b)}$ tends to be predominantly located in a certain elliptical region of the time-frequency plane centered at $t = b$ and $\omega = \omega_0 / a$. The area of these localization regions is the same for all templates $((a \cdot \Delta_\psi) \times (\Delta_{\hat{\psi}} / a))$ and is constrained by the uncertainty principle. Thus, by measuring the correlation between the signal and each wavelet template, we obtain a characterization of its time-frequency content (scalogram). The main difference with the short-time Fourier transform is that the size of the analysis window is not constant for it varies in inverse proportion to the frequency. This property enables the wavelet transform to zoom in on details, but at the expense of a corresponding loss in spectral resolution. In this respect, we should note that most biomedical signals of interest include a combination of impulse-like events (spikes and transients) and more diffuse oscillations (murmurs, EEG waveforms) which may all convey important information for the clinician. The short-time Fourier transform or other conventional time-frequency methods are well adapted for the latter type of events but are much less suited for the analysis of short duration pulsations. When both types of events are present in the data, the wavelet transform can offer a better compromise in terms of localization. This may explain its recent success in biomedical signal processing. Recent examples of applications where time-frequency wavelet analysis appears to be particularly appropriate are the characterization of heart beat sounds [22, 21, 31], the analysis of ECG signals including the detection of late ventricular potentials [21, 16, 28, 39] , the analysis of EEGs [38, 37, 50], as well as a variety of other physiological signals [36].

B. Wavelets as a multi-scale matched filter

In essence, the continuous wavelet transform performs a correlation analysis, so that we can expect its output to be maximum when the input signal most resembles the analysis template $\psi_{(a,b)}$. Consider the measurement model $f(x) = \varphi_a(x - \Delta x) + n(x)$ where $\varphi_a(x) = \varphi(x/a)$ is a known deterministic signal at scale a, Δx an unknown location parameter, and $n(x)$ an additive white Gaussian noise component. Classical detection theory tells us that the optimal procedure for estimating Δx is to perform the correlation with all possible shifts of our reference template and to select the position that corresponds to the maximum output (matched filter). Therefore, it makes sense to use a wavelet transform-like detector whenever the pattern φ that we are looking for can appear at various scales.

If the noise is correlated instead of white, then we can get back to the previous case by applying a whitening filter. Interestingly, the wavelet-like structure of the detector is preserved exactly if the noise has a fractional brownian motion structure. Specifically, when the noise average spectrum has the form $\phi_n(\omega) = \sigma^2 / |\omega|^\alpha$ with $\alpha = 2H+1$ where H is the Hurst exponent, we can show that the optimum detector $\psi(x)$ is proportional to the αth fractional derivative of the pattern φ that we want to detect. Consequently, for $H>0$, the optimal detector is an admissible wavelet even if the initial template $\varphi(x)$ is not (e.g. it is a lowpass function). For example, the optimal detector for finding a Gaussian in $O(\omega^{-2})$ noise is the Mexican hat wavelet (2nd derivative of a Gaussian). As suggested by Strickland, this is perhaps one of the main reasons why the wavelet transform works well for detecting microcalcifications in mammograms [7, 32, 41].

3. WAVELET BASES

Wavelet bases provide a non-redundant decomposition of a signal in terms of the shifts and dilations of ψ (hierarchical or pyramidal transform). Hence, it is possible to represent a signal through its wavelet expansion

$$f=\sum_i \sum_{k\in Z} c_{i,k}\psi_{i,k} \tag{4}$$

where the $c_{i,k}=\langle f,\psi_{i,k}\rangle$ are the wavelet coefficients (scale index *i*, and position index *k*). There are also non-hierarchical versions (wavelet packets, *M*-band perfect reconstruction filterbanks) that constitute a direct extension of the traditional block transforms (Fourier, DCT, etc..). The important point for our purpose is that, in the discrete case, the decomposition formula (4) provides a one-to-one representation of the signal in terms of its wavelet coefficients (reversible linear transformation). This makes WB well suited for any of the tasks for which block transforms have been used traditionally: data compression, data analysis (decorrelation), and data processing (generalized filtering). Wavelets, however, may present certain advantages because they can improve the signal-to-noise ratio, while retaining a certain degree of localization in the time (or space) domain.

A. Data Compression

Data compression can be achieved by quantization in the wavelet domain, or by simply discarding certain coefficients that are insignificant. This form of orthogonal (or close-to-orthogonal) decomposition has been used effectively for image compression [25, 4, 14, 40]. Traditionally, this has been one of the primary applications of wavelets.

B. Data Processing: wavelet denoising

One of the first application of the wavelet transform in medical imaging was for noise reduction in MR images [54]. The approach proposed by Weaver et *al.* was to compute an orthogonal wavelet decomposition of the image and apply the following soft thresholding rule on the coefficients $c_{i,k}=\langle f,\psi_{i,k}\rangle$:

$$\tilde{c}_{i,k}=\begin{cases} c_{i,k}-t_i & c_{i,k}\geq t_i \\ 0 & |c_{i,k}|\leq t_i \\ c_{i,k}+t_i & c_{i,k}\leq -t_i \end{cases} \tag{5}$$

where t_i is a threshold that depends on the noise level at the *i*th scale; the image is then reconstructed by the inverse wavelet transform of the $\tilde{c}_{i,k}$'s. This is essentially the wavelet shrinkage denoising method later systematized by Donoho and Johnston [18, 17], as well as DeVore and Lucier [15]. This algorithm is extremely simple to implement and works well for moderate levels of noise. Asymptotically (as the scale goes to zero and as the noise energy gets distributed over more and more sample values), it has some interesting min-max optimality properties for a relatively large class of signals [17].

The approach can easily be taken one step further by considering more general pointwise non-linear transformations $\tilde{c}_{i,k}=F(c_{i,k})$. Consider the measurement model $c_{i,k}=c^s_{i,k}+n_{i,k}$ where $c^s_{i,k}$ denotes the wavelet coefficient of the noise-free signal and $n_{i,k}$ is an independent noise component. In principle at least, one could apply the optimal Bayesian estimation rule : $\tilde{c}_{i,k}=E[c^s_{i,k}\mid c_{i,k}]$, which minimizes the mean square error. This of course requires the knowledge of the *a posteriori* probability density function $p(c^s\mid c)$, which depends on our *a priori* knowledge on $c^s_{i,k}$ ($p(c^s)$), and on the noise distribution ($p(n)=p(c\mid c^s)$). We can also constrain ourselves to the class of linear estimators, and derive the optimal linear estimate

$$\tilde{c}_{i,k}=\left(\frac{E[(c^s_{i,k})^2]}{E[(c^s_{i,k}+n_{i,k})^2]}\right)\cdot c_{i,k}, \tag{6}$$

which has the form of a generalized Wiener filter. This particular algorithm was first proposed by Bertrand et al. for the processing of evoked response potentials (ERPs) [5]. These are very noisy signals with a strong deterministic component. Because ERPs are usually acquired using multiple trials (typ. 100-600 repetitions), the optimal weighting factors in (6) can be estimated on a coefficient-by-coefficient basis in an initial training phase, or even updated recursively. In this particular application, the wavelet transform appears to be superior to the Fourier transform, the latter being optimal only when both the signal and noise are stationary (conventional Wiener filter).

C. Data Analysis: detecting changes in fMRI

Functional neuroimaging is a fast developing area aimed at investigating the neuronal activity of the brain in vivo. The data for those studies is provided by positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). PET measures the spatial distribution of certain function-specific radiotracers injected into the bloodstream prior to imaging. A typical example is the measurement of cerebral glucose utilization with the tracer [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG). fMRI, which is a more recent technique, allows for a visualization of local changes in blood oxygenation believed to be induced by neuronal activation. It is substantially faster than PET and also offers better spatial resolution. Yet, there is still disagreement among specialists concerning the exact nature of the biological processes that produce the observed changes in the MR signal.

The functional images obtained with those two modalities are extremely noisy and variable, and their interpretation requires the use of statistical analysis methods [51]. What is typically of interest is the detection of the differences of activity between different groups of subjects (e.g. normal versus diseased) or between different experimental conditions with the same subject (e.g. rest versus word generation). In either case, the variability of the signal is such that multiple subjects or repeated trials are required in each subgroup.

The first step in this analysis is to register the various images so that they can be compared on a pixel-by-pixel basis [42]. The second step is to compute the difference between the aligned group averages and perform the statistical analysis. Testing in the image domain directly is difficult because of the amount of residual noise and the necessity to use a very conservative significance level to compensate for multiple testing (one test per pixel!). A better solution is to perform the testing in the wavelet domain [35, 33, 51]. The main advantage is that the discriminative information, which is smooth and well localized spatially, becomes concentrated into a relatively small number of coefficients, while the noise remains evenly divided among all coefficients. In addition, the number of statistical tests can be reduced considerably by first identifying the few wavelet channels that contain significant differences. A recent application of this technique to fMRI is presented in [34].

4. EXTENSION OF THE KARHUNEN-LOÈVE TRANSFORM

One stage of the fast wavelet transform algorithm can be conveniently described as a multivariate filtering operation using the so-called *polyphase* representation [53]. The corresponding filterbank system is shown in Fig. 1.

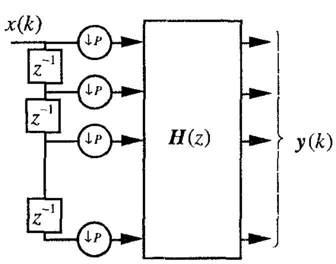

Fig. 1: Polyphase representation of a P-band wavelet analysis filterbank.

In this diagram, $x(k)$ represents the input signal and the y's are the various wavelet channels after one level of decomposition. In the standard dyadic case, there are only two channels (P=2), but the concept is also valid for larger values of P (P-band perfect reconstruction filterbank) [52, 53]. It turns out that the transformation is orthogonal if and only if the $P \times P$ transfer function matrix $\boldsymbol{H}(z)$ satisfies the paraunitary condition:

$$\boldsymbol{H}(z) \cdot \boldsymbol{H}(1/z) = \boldsymbol{I}_P, \qquad (7)$$

where $\boldsymbol{I}_P$ is the $P \times P$ identity matrix. Note that for traditional block transforms, the matrix $\boldsymbol{H}(z)$ does not depend on z (i.e., the various blocks are processed independently of each other). In order to design the optimal wavelet transform for a given class of input signals, it is therefore natural to seek the paraunitary matrix $\boldsymbol{H}(z)$ that provides the maximum energy compaction in the wavelet domain [44]. If the matrix $\boldsymbol{H}$ is constrained to be real (no delays), the solution corresponds to the classical Karhunen-Loève transform (KLT). If we allow for more general structures (for example, $\boldsymbol{H}(z)$ is an N-point FIR transfer function), we can get better results but the filter optimization subject to constraint (7) is a rather difficult task [44, 30, 6, 13]. One interesting property of the optimal solution is that the transformed components are uncorrelated; however, this is not a sufficient condition for optimality, in contrast with the standard KLT [44].

If we do not impose any order constraint on $\boldsymbol{H}(z)$, it is possible to derive the optimal solution analytically for any given wide sense stationary process with spectral power density $S_x(\omega)$. The two channel case is considered in [45]; the more general P-band case is treated in [43] using an elegant principal component formulation in the frequency domain. In each case, the solution depends on the spectral characteristics of the input signal and has the form of an ideal filter with pure "on" and "off" frequency bands. If the power spectral density is non-increasing, then the optimal solution is the ideal filterbank with P uniformly-spaced subbands. Interestingly, there are a number of wavelet transform constructions that converge asymptotically to this limit. The better known example is the family of Battle-Lemarié spline wavelets which converge to an ideal bandpass filter as the order of the spline goes to infinity [24, 48, 2]. Daubechies wavelets also exhibit similar convergence properties [23]. This partially explains why higher order wavelets usually result in smaller approximation errors.

These unconstrained solutions are primarily of interest from a theoretical point of view. For example, they can be very useful for deriving asymptotic bounds on the best performance achievable (e.g. coding gain over PCM) [12]. They are less relevant for implementation purposes because of the disadvantages of ideal filterbanks (slowly decaying impulse responses, Gibbs oscillations). This provides a good motivation for investigating more constrained solutions. As far as we know, there is not yet any general procedure for designing optimal FIR wavelets that is entirely satisfactory; this is currently an active area of research.

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