Data Weighting for Principal Component Noise Reduction in Contrast Enhanced Ultrasound

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Abstract. Pulse inversion ultrasound is a mechanism for preferentially displaying contrast agent in blood vessels while suppressing signal from tissue. We seek a method for identifying and segmenting areas of the liver with similar statistically significant time intensity curves. As a first step in this process, a method of weighting Rayleigh distributed ultrasound image data before principal components analysis is presented. Simulation studies show that relative mean squared error can be reduced by 14% when the correct number of dimensions is selected. Our method is tested on an *in vitro* ultrasound phantom showing slightly increased error suppression, and is demonstrated on a clinical liver scan, showing decreased correlation between signals in the low intensity range.

1 Introduction

Pulse inversion imaging has been shown to be useful in the diagnosis of several varieties of liver lesions [1]. The introduction of small spheres of encapsulated gas called microbubbles can provide a means of detecting intravascular contrast agent independently of tissue. It is commonly used clinically to differentiate between areas of contrast and tissue to characterize the vasculature of the liver [2].

Liver screening based on contrast enhanced ultrasonography is regularly performed at Toronto General Hospital for those who are at increased risk of developing cancer of the liver. Acquisition is sensitive to the position and motion of the ultrasound transducer and the scanner settings. Diagnosis is also sensitive to the experience of the radiologist and the conspicuity of fine structures in the noisy image. We seek a means of segmenting the arterial and portal blood flow of the liver over time to aid in diagnosis.

Multidimensional techniques such as Principal Components Analysis (PCA) and Factor Analysis (FA) have been proven effective at identifying time-intensity curves from series of images [3][4]. The dual blood supply of the liver makes factor analysis a good tool candidate for improving the interpretability of these screenings.

Here we outline some of the properties of pulse inverted ultrasound images. Next, we propose a statistically weighted method of performing PCA for purposes of dimensionality reduction. Its effect on an *in vitro* blood flow study is given, and finally its smoothing effect on *in vivo* human liver images is demonstrated.

2 Orthogonal Analysis

The first step in most factor analysis studies is to reduce noise while defining the study subspace representing physical changes. PCA performs this function for us by obtaining the directions of maximum total variance among the data. Applied blindly, this technique captures the features of maximum variation, signal or otherwise, in the data sets. Suppose we decompose our data set as follows:

$$D = UV + \epsilon \quad (1)$$

where D is the $m \times n$ matrix composed of the measured m images aligned as columns and n pixels (rows). D is factored into two components, a $m \times f$ matrix U representing a map of spatial locations, and a $f \times n$ matrix V representing relative time intensity curves. n is the number of pixels in an image or region of interest (ROI) and m is the number of measurements taken at each pixel. f is the number of retained principal components (PCs). When $f = n$, U and V are trivially assigned to perfectly represent the measured data; and ϵ is zero. Typically, f is chosen based on the relative contribution to variance as expressed by each successive eigenvalue in the decomposition.

It has been argued that PCA may not necessarily capture the relevant variance in non-gaussian distributed data sets[5]. In these cases, ignorant orthogonal analysis will capture a biased subset of data. So, a blind PCA operation on this type of ultrasound data will capture the two types of variance: that which is caused from intensity changes due to changes in contrast agent concentration, and that which arises naturally due to speckle at each level of concentration. We seek a method of separating out variance due to concentration changes of contrast agents to more accurately capture the clinically relevant data. In this way, we will eliminate the potential variance bias of PCA reduction.

2.1 Ultrasound Weighted PCA

Microbubbles have a tendency to resonate nonlinearly when exposed to an ultrasound field returning a nonlinear reflected pulse. In pulse inversion imaging, the transducer is configured to send and receive two successive pulses that are inversions of each other. The sum of reflected waves from linearly reflective tissue will produce a null signal, while the same operation applied to the signal reflected by microbubbles will produce a non-zero signal (Table 1).

Ultrasound imaging suffers from some fundamental physical limitations affecting the signal-to-noise ratio of resulting images. One particular component of limitation is due to speckle, which is a signal seen in ultrasound images arising from coherent interference from scatterers smaller than the wavelength of the transmission pulse. An ensemble of microbubbles approximately $1 - 5\mu m$ in size contributes a signal with speckle characteristics. We are interested in isolating signal changes in the image due to concentration changes of microbubbles.

Table 1. Pulse Inversion Imaging: the sum of two linear inverted tissue echoes cancel while the sum of the same nonlinear echoes from bubbles do not

	Transmitted Pulse	Linear Tissue Echo	Nonlinear Bubble Echo
Pulse
Inverted Pulse
Sum

2.2 Weighted PCA for Rayleigh Distributed Data

Cochran and Horne showed that there are data transforms that may be applied prior to the PCA operation that can aid in the significance of the resulting PCs [6]. Šámal[7] has written a comprehensive review of methods for correspondence analysis. Benali et al. used correspondence analysis [5] to split data between a physical model and a statistical model. Keenan and Kotula have recently shown [8] that this type of blind variance separation can be applied to Poisson noise data resulting from surface mass spectroscopy data. These transforms make an assumption about the expected variance of a given error or data element. The variance of each data element d_{ij} is factored into two factors:

$$var(d_{ij}) = g_i h_j \quad (2)$$

where g_i and h_j represent contributions to the variance from as a result of time i at pixel j . Variance due to spatial interference patterns is assumed to be independent of time. Although the expected velocity of the bubbles and the detector is small, it is sufficient to decorrelate them. Cochran and Horne [6] showed that the optimally weighted data matrix D_W is

$$D_W = (aG)^{-1/2} D (bH)^{-1/2} \quad (3)$$

where a and b are arbitrary constants, and G and H are diagonal matrices containing the elements g_i and h_j . Scalar constants a and b are added for convenience, as the linear scaling does not affect the variance of the data.

A priori information in factor analysis helps decompose our signal into those representing directions of change in the data set. The received signal from an ensemble of nonlinear coherent scatterers can be modeled as a zero mean multivariate normal distribution in the imaginary plane[9]. The magnitude of the envelope-detected signal forms a Rayleigh distribution [10], with β representing

the variance of each of the underlying normal distributions. The probability distribution function is:

$$p(x) = \begin{cases} \frac{x}{\beta^2} e^{\frac{-x^2}{2\beta^2}} & \beta, x \geq 0 \\ 0 & x < 0 \end{cases} \quad (4)$$

Estimates of parameter $\hat{\beta}$, mean ($\hat{\mu}$) and variance ($\hat{\sigma}^2$) can be estimated from sample data using the following equations:

$$\hat{\beta} = \sqrt{\frac{1}{2N} \sum_{i=1}^N x_i^2} \quad (5) \quad \hat{\mu} = \hat{\beta} \sqrt{\frac{\pi}{2}} \quad (6) \quad \hat{\sigma}^2 = \frac{4-\pi}{2} \hat{\beta}^2 \quad (7)$$

We can see from the above equations that the intrinsic variance of the signal can be estimated from the data set provided we have a large number of samples N . We can estimate G and H by using our variance estimates of the Rayleigh distribution outlined in 7. Combining 7 and 5 we obtain

$$\text{var}(d_i) = g_i = \frac{4-\pi}{2} \left(\sqrt{\frac{1}{2n} \sum_{j=1}^n d_{ij}^2} \right)^2 = \left(\frac{4-\pi}{4} \right) \frac{1}{n} \sum_{j=1}^n d_{ij}^2 \quad (8)$$

Similarly, (9)

$$\text{var}(d_j) = h_j = \frac{4-\pi}{2} \left(\sqrt{\frac{1}{2m} \sum_{i=1}^m d_{ij}^2} \right)^2 = \left(\frac{4-\pi}{4} \right) \frac{1}{m} \sum_{i=1}^m d_{ij}^2 \quad (10)$$

So that, if we set $a = b = (4 - \pi)/4$ then

$$aG = \frac{1}{n} \text{diag} \left(\sum_{j=0}^n d_{ij}^2 \right) \quad (11)$$

$$bH = \frac{1}{m} \text{diag} \left(\sum_{i=0}^m d_{ij}^2 \right) \quad (12)$$

which are simply mean squared value of the rows and columns, respectively. It is now simple to determine the weighting matrix by inverting the square root of the row and column averages, above.

$$D_W = \frac{1}{mn} (\text{diag}(\sum_{j=0}^n d_{ij}^2))^{-1/2} D (\text{diag}(\sum_{i=0}^m d_{ij}^2))^{-1/2} \quad (13)$$

The original data set can be estimated from the principal components of the weighted matrix, U_W and V_W by inverting the weighting matrices $U = (aG)^{1/2} U_W$ and $V = V_W (bH)^{1/2}$ ignoring reconstruction error ϵ . This inversion operation is simple as the weighting matrices are diagonal. These relationships will be used to weight our data, perform PCA, and subsequently undo the transform on the resulting components for display.

3 Simulated Data

To test the properties of the weighted principal components analysis above, a simulated ultrasound data set was constructed under the assumption of Rayleigh distributed signals. A series of images was constructed with four different areas enhancing with a different, but known time intensity curve. These image areas were multiplied by the corresponding curves as shown in Figure 1.

Fig. 1. Time intensity curves (a) and image areas used. (c) is an image from the simulated data set where each area is Rayleigh distributed.

Four curves are shown, of which only three are linearly independent, so three principal components are expected. To simulate ultrasound image data, the resulting image series was converted into Rayleigh distributed data, with each data point having a mean equal to the original value of the pixel. An image from the set appears is shown in Figure 1(c), after scaling for display. PCA was performed on the simulated noisy data set and the weighted noisy data set as explained above. The result of the PCA was compared to the noise-free data set generated, and the relative mean squared error ($RSME = \Sigma(D - D_{true})^2 / \Sigma D_{true}^2$) was calculated after reconstructing the data for varying dimensionalities.

Fig. 2. Reconstruction error using Principal Components of the two data sets

The reconstruction error from three or more principal components is less for the weighted data than the unweighted data. If two or less principal components are used, the unweighted data produces a better estimate of the original data.

Fig. 3. Image from phantom study bidirectional flow through overlapping tubes (a) and RMS error in the phantom study (b)

The error values actually increase beyond the ideal number of components. This same basic error structure was found for other curves as well; always at a minimum at the real number of principal components, independently of the shape of the curves. At least a 14% improvement in RMS error is found when the minimum number of PCs are retained.

4 Phantom Results

To test this method *in vitro*, a dilution of microbubbles (Definity, DuPont Pharmaceuticals, Billerica, Massachusetts) in water (approximately 0.1mL/L) was directed through polyethylene tubing suspended in water. Images were captured using an ultrasound scanner (AplioTM, Toshiba Medical Systems, Tokyo, Japan) in pulse inversion mode. Both tubes were designed to cross in the field of view. Images were obtained with a 6 MHz rectilinear transducer array (PLT 604AT) at a maximum depth of 3 cm with the focus at that depth, $\text{MI}=0.04$, $2\text{DG}=95\text{dB}$, $\text{DR}=45\text{dB}$. A sample image was scaled for display and is shown in figure 3(a).

The images were processed as outlined above, using both the weighted PCA and unweighted PCA. A region of interest was placed on the image above the features, where no signal is expected. PCA smoothing was performed on the data, and the ability of each method to reduce noise in the ROI was measured by calculating the mean intensity. The results are presented in figure 3(b). The magnitudes in this application were obtained after scanner post-processing of the envelope-detected data.

5 Clinical Application

This technique was applied to clinically obtained contrast enhanced ultrasound scans of the liver. A region of interest was manually delineated around the liver of the patient, and a series images taken over 40 seconds post contrast injection

Fig. 4. Late enhancement frame (a) and time intensity curves for a typical background and lesion pixel (b). The loadings (V) of the first two PCs is plotted (c).

were analyzed using the above techniques. Images are reconstructed using 3 principal components.

The largest difference between the weighted and nonweighted PCA smoothing can be seen on the images resulting from only 2 PCs. In these images, the weighted PCA smoothes the image more in regions of high intensity. It is clear that using only 2 PCs has left out some important features of the image, most notably the dark region in the centre of the lesion that has been identified as a necrotic core. This is improved when using 3 PCs, and using 4 PCs or more shows few discernible differences between the images. The corresponding time intensity curves show a marked decorrelation in signal from lesion and background.

Fig. 5. The same frame as in figure 5 after PCA smoothing (top) and weighted PCA smoothing (bottom). Time intensity curves for same pixel as in 5(right).

6 Discussion and Conclusion

There is some agreement between theory and our *in vitro* experiments where error can be measured. The minimum RMS error occurs at the correct number of principal components. Weighted PC noise reduction only shows a slight difference in the ability to reduce noise in the phantom study. When enough dimensions are retained, our technique has proven to capture noiseless data more accurately. We see this effect in our *in vivo* study in the ability of the method to more accurately smooth background pixels while maintaining contrast in 'feature' pixels.

We have outlined some of the theory and shown the clinical applicability of our weighted PCA smoothing technique. Although only a first step in a goal of mapping time intensity curves in the liver resulting from hepatic and portal blood supplies, some properties of PCA smoothing have proved useful. We can see that weighted PCA can perform better for Rayleigh distributed signals by removing the inherent variance bias towards larger signal intensities, and thus smoothing more uniformly over the image. Preliminary clinical data indicates that we can improve on the ability to identify subtle lesions in the data that may otherwise have been lost in the background noise.

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