Local phase significance estimated with uncertainties to detect fibrotic regions from *in vivo* pancreatic cancer images

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Abstract. Pancreatic ductal adenocarcinoma (PDAC) is the fifth leading cause of death among cancer cases. One of the most debated questions is whether fibrosis, which is linked to resistance to treatment, is promoted by the so called pancreatic stellate cells (PSC). Pre-clinical research currently uses ultrasound (US) images in an attempt to answer this question. However, such images often have poor signal-to-noise ratio (SNR) and limited resolution, so relying solely upon visual inspection, their target might easily be missed. To further investigation of this question, we are attempting to identify fibrotic regions, currently in ultrasound images, with minimal user interaction. To achieve this, we adopt a multi-scale framework and estimate local phase (LP) significance based on feature uncertainty and LP coherence: (1) images are decomposed into multiple scales using the Mellor-Brady filter, (2) uncertainties from normalised covariance matrices at each scale are estimated, (3) noise variances are calculated using continuous intrinsic dimensionality and non-parametric probability density estimation, and (4) local phase significance is calculated as a normalised weighted sum, with uncertainty weights from (2). Initial results of this method are demonstrated on pre-clinical PDAC images to identify regions that represent fibrosis.

1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fifth leading cause of death among cancer cases in UK, with only 3% of patients surviving to 5 years, despite it being only the 11th most common cancer. There is therefore a need for substantial improvement to currently available treatment planning tools, such as predicting the outcome and monitoring of the tumour response to therapy. Recently, attention has increasingly been focussed on the role of the tumour microenvironment (TM), "the stroma", which makes up more than 60 $\%$ of the pancreatic tumour mass as a result of the abundant desmoplastic reaction. Desmoplasia is the formation of adhesion and fibrous connective tissue within the tumour and has been linked to the presence of pancreatic stellate cells (PSC). Although fibrotic regions have been associated with poor treatment outcome [1], currently no defined imaging and/or image analysis protocol has been defined to quantify its presence. Images used for assessment, such as ultrasound (US) and Magnetic Resonance Imaging (MRI), often have limited spatial resolution and are corrupted by noise. These factors limit the identification of significant structural organization of features using state-of-the-art texture description and feature detection techniques.

Robust structure descriptors are invariant to image scaling, rotation, translation, variable lightning conditions and process noise. One particular approach that satisfies these requirements is to use local phase (LP) based descriptors from a multi-scale decomposition of the image via an isotropic filter and its generalized quadrature pair. However, the fact that LP values are significant only if there is congruence of the phases (PC) over multiple scales is often neglected.

The original definition of PC has been developed since its original formulation by Morrone and Owens [2]. However, even the currently accepted form has severe limitations in the presence of noise, including noise-like high frequency signal components. Morrone and Owens defined PC at each location as the amplitude weighted mean local phase angle of all the Fourier series components at that point, and proposed to identify PC from the extremum points of local energy (LE) [2]. While this is of interest in defining and finding features in noise-free images, as was reported in [3], it is of limited value when applied to real images with brightness/contrast variation and loses the benefits offered by LP of being intensity invariant. The Morrone and Owen's energy model has been extended to 2D to be more robust to noise effects, given a noise model has been identified and calculated in different orientations [4] [5]. The use of energy limits this approach, due to the intrinsic and substantial sensitivity of LE to intensity variations.

Our contribution is to propose a measure to estimate local phase significance values based on feature certainty and local coherence of LP values, and identify local noise characteristics from multiple scales. To this end, we use the eigenvalues of local covariance matrices and a probabilistic formulation of continuous intrinsic dimensionality to identify how much we believe the image data belongs to the class of "real" or noise corrupted signal class. This then allows us to give a measure of local phase values from a small neighbourhood and their significance. We demonstrate the possible use of

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this method in pre-clinical *in vivo* PDAC US images to support the hypothesis that PSCs promote tumour development, which partly manifests in excessive fibrosis formation. As a result, control and PSC co-cultured PDAC tumour images are compared.

2 Methods

2.1 Experimental data and image acquisition

An orthotopic nude mouse model of pancreatic cancer was used. Half the mice were surgically injected with 2 x 10^6 (in 30μl DMEM medium) human Panc-1 cells only, while half were co-injected with a 1:1 proportion of human Panc-1 pancreatic adenocarcinoma cells and LTC-4 rat PSC cells of the same amount to the pancreatic tail.

Data were collected on a preclinical Vevo 770, Visualsonics, Toronto, Canada US scanner in Bmode with a transmit frequency of 40Hz, movie frame rate 34Hz and a Field of View (FOV) of 10 mm x 10 mm. No Time Gain Compensation (TGC) was adjusted at the time of data acquisition; as a result, intensity variations at greater depths are observable, but which was taken in account during our analysis. The effective image resolution is 0.02 mm x 0.02 mm on a 500 x 500 pixel grid. Tumours were manually segmented using ITK-SNAP 1.6.0.1.

2.2 Image analysis methodology

In this section we describe the algorithm we have developed to estimate local phase values, and which is outlined in Figure 1.

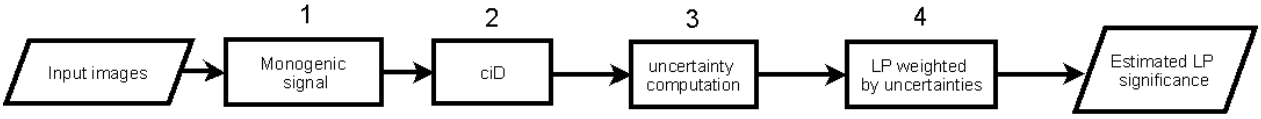

Figure 1. Algorithm to estimate local phase significance values. For explanation of each step, refer to the text.

1. Images were first decomposed into consecutive frequency bands using the Mellor-Brady filter [6], and local descriptors extracted using the monogenic signal [7].

The monogenic signal is a generalization to nD using the Riesz transform of the 1D analytic signal (which is defined using the Hilbert transform). In 2D (for example), denote the bandpassed 2D input signal at scale s as $b(\overline{x}, s)$, $\overline{x} \in \mathbf{R}^2$. Then, the monogenic signal is defined as:

$$\mathbf{M}(b(\overline{x}, s)) = (b(\overline{x}, s), \mathbf{R}\,(b(\overline{x}, s)))\,, \tag{1}$$

where $\mathbf{R}$ denotes the Riesz transform, and its components in 2D are defined as

$$(r_1(\overline{x}, s), r_2(\overline{x}, s)) = (\mathbf{Re}(\mathbf{R}(b(\overline{x}, s)), \mathbf{Im}(\mathbf{R}(b(\overline{x}, s)))\,. \tag{2}$$

Local energy (LE), phase (LP) and orientation (LO) are local descriptors of the image that enable separation of the intensity dependent energy from structural phase information and orientation of the underlying geometry.

Here, we denote these as *raw* image descriptors in order to differentiate them from the new estimates introduced in this paper at point (5). (Note that indices $(\overline{x}, s)$ were ignored in eq. 3 due to space limit.)

$$E:\ \mathcal{E}^{\text{raw}} = \sqrt{b^2 + r_1^2 + r_2^2} \quad LP : \psi^{\text{raw}} = \mathbf{arctg}\left(\frac{b}{\sqrt{r_1^2 + r_2^2}}\right) \quad LO : \phi^{\text{raw}} = \mathbf{arctg}\left(\frac{r_2}{r_1}\right). \tag{3}$$

2. We used the continuously-valued intrinsic dimensionality (cid) to obtain the probabilities of how much we believe a region is homogeneous, simple 1D and 2D structures and a mixture of these in the form of texture. Cid of the input image structures was calculated according to the theory presented in [8]. This method is different from that of, e.g. the Harris corner detector, in that no judgement is made about which category a pixel within an image patch belongs to. In contrast, it associates three class probability values to each spatial location, which then can be used as prior probabilities to a higher level processing unit.

Since this method relies on accurate local energy and orientation, we replaced the structural tensor estimations (as was suggested in the original work) with the structural descriptors derived from the monogenic output from point (1). Local orientation from the monogenic signal was estimated from a single scale, selected empirically, which is application specific. Given the nature of our noisy US images the 2D cid estimate using local Gaussian smoothing eliminates small cues. To avoid this, we replaced this estimation step by the mode of 5×5 neighbourhood probability density functions (pdf) calculated with a 2D non-parametric (NP) windows method [9]. This allows to evaluate image intensity statistics taking in account the relationship between neighbouring pixels, as opposed to the standard histogram based methods.

There are three outputs from this block: ci0D, ci1D and ci2D, which correspond to probabilities whether the underlying signal belongs to the class of ci0D (i.e. homogeneous), ci1D (i.e. line, edge like), or ci2D (i.e. corner, texture) respectively. These give a good approximation to how much we believe the variance in a small image patch derives from it being a complex (e.g. 2D) structure or noise.

Noise variances were estimated by identifying homogeneous regions, such that $p(ci0D) > 0.95$. Local standard deviations in a neighbourhood of 3 x 3 are calculated and the noise variance for an image is then estimated as the mode of the pdf (estimated with NP windows method) from local variances. Noise covariance matrices are then estimated as $\sigma(i,j,s) \cdot I$, where I denotes the identity matrix.

3. Geometric feature uncertainty generally refers to the degree to which an interest point can be localized. An accepted method is to estimate the normalized covariance by the inverse Hessian. Then homogeneous regions result in high uncertainty, while fast changes around the feature point result in high confidence. To date, we have estimated local uncertainties with the inverse Hessian (H(i,j,s)) at each scale, as in the Harris corner detector. This is then calculated using a differential method as:

$$\begin{pmatrix} \sum_{(k,l)=-M}^{M} w(i,j) I_i^2(i+k,j+l,s) & \sum_{(k,l)=-M}^{M} w(i,j) I_i(i+k,j+l,s) I_j(i+k,j+l,s) \\ \sum_{(k,l)=-M}^{M} w(i,j) I_j(i+k,j+l,s) I_i(i+k,j+l,s) & \sum_{(k,l)=-M}^{M} w(i,j) I_j^2(i+k,j+l,s) \end{pmatrix}$$

where a neighbourhood of (2M+1) $\times$ (2M+1), $M = 1$, was used. Partial derivatives were approximated using finite differences which at interior positions were calculated as centered differences, while we took the forward difference at the edge points.

The output of this stage gives the weight of how much we believe the LP value contributes to the real LP measure in form of the eigenvalue magnitudes $u(i,j,s) = \sqrt{e_1^2 + e_2^2}$, where e_1 and e_2 denote the two eigenvalues, s is scale and $(i,j) \in \overline{x}$ image pixel coordinates (Figure 3).

4. Better conditioned LP values are estimated by combining LP^{raw} over a small neighbourhood weighted by the uncertainties from (3)

$$\psi(i,j,s) = \frac{\sum_{(k,l)=-M}^{M} u(i+k,j+l,s)\psi^{\text{raw}}(i+k,j+l,s)}{\sum_{(k,l)=-M}^{M} u(i+k,j+l,s)}, \tag{4}$$

where $u(i,j,s)$ is the uncertainty index from (3) and $\psi^{\text{raw}}(i,j,s)$ denotes the local phase output from (1) at position i,j and scale s respectively. Significance values are then approximated by fitting first and second order polynomials across scales.

3 Results

US images of PDAC tumour samples were assessed both from the control and the PSC injected group (see Sec. 2.1). Since tumour formation was considerably lower in the control mice, we demonstrate our approach on one control tumour and two tumours that developed in the presence of PSC.

Comparison between the feature points detected by the Kovesi PC measure and the method proposed here is presented

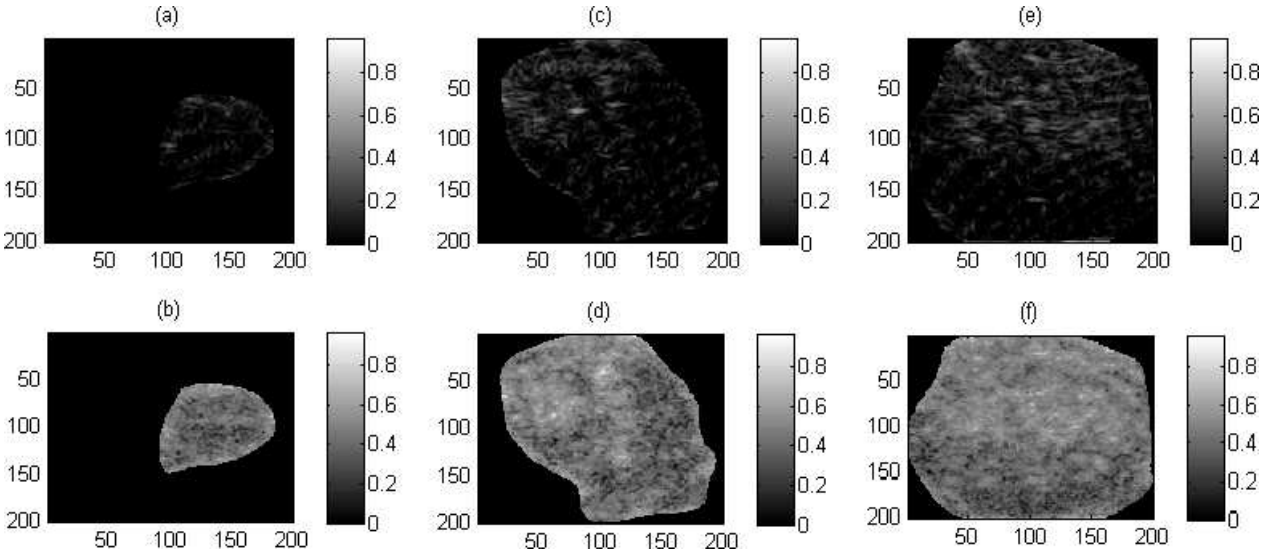

Figure 2. Comparison between fibrotic regions highlighted by the Kovesi PC measure and the method proposed here. Top row shows the Kovesi PC measure, while bottom row the results from our method. No postprocessing of the images has been performed, except that the sign of the output from our method has been flipped to aid comparison. (a) and (b) shows a control tumour, while the rest are samples from the PSC injected group. (Figure to be inspected in colour.)

in Figure 2. Note the differences between the structural organization between the two approaches, for which the same colormap has been used to present the results for the two methods. These show that the Kovesi type PC measure is highly correlated with image energy (high intensity), which in our example also means that features from noise corrupted US images will be missed (such as shown in this paper).

Fibrotic regions in PC uncertainty maps (Figure 3 (j)-(l)) were visually assessed and compared to previous methods by an expert clinical scientist. These maps (in coloured version) were found to give a higher fidelity in identifying fibrotic regions than the original images (Figure 3 (j)-(l)) and Kovesi type PC values. The brighter region, that is the region corresponding to phase significance values above approximately 0.7 is expected to represent fibrosis and which is present to a large extent in tumours co-cultured with PSC, however very little can be observed in the control tumours. We additionally show the corresponding local phase maps from a single scale (d)-(f) and the uncertainty maps (g)-(i). Note that the local phase maps and the computed certainty maps are not a scaled version of each other. Further, the uncertainty maps computed from the Hessian can not replace the proposed method due to the presence of US speckle, excessive noise and the elongated nature of the fibrotic structures (3), which prevent this.

4 Discussion

An improved way of estimating local phase significance from multiple scales was described to aid the detection of fibrotic regions from pre-clinical PDAC US images. This method relies on uncertainties estimated from local covariances and continuous intrinsic dimensionality to estimate the fidelity of LP values.

Although no previous shape characterisation of the fibrosis of the pancreas has (to our knowledge) been reported, geometrical observations of the fibrotic elements here are in agreement with observations recorded from hepatic samples, which is the closest point of comparison.

We are aware that this method may lead to a suboptimal solution in this estimation process at several stages since all the steps are prone to be perturbed by noise effects. These include (1) noise variances that rely on identified homogeneous regions; (2) intrinsic dimensionality itself is influenced by noise, that is, increasing noise levels shifts the true iD towards i2D as has been reported in [8]; and (3) covariances estimated using differential methods are also perturbed by noise.

In conclusion, a method has been proposed to identify fibrotic regions in pre-clinical PDAC images using local phase significances. This constitutes the first step in a higher level feature and/or feature based classification process. Finally, it has not escaped our attention that our proposed numerically well conditioned, approximately noise free, estimates of

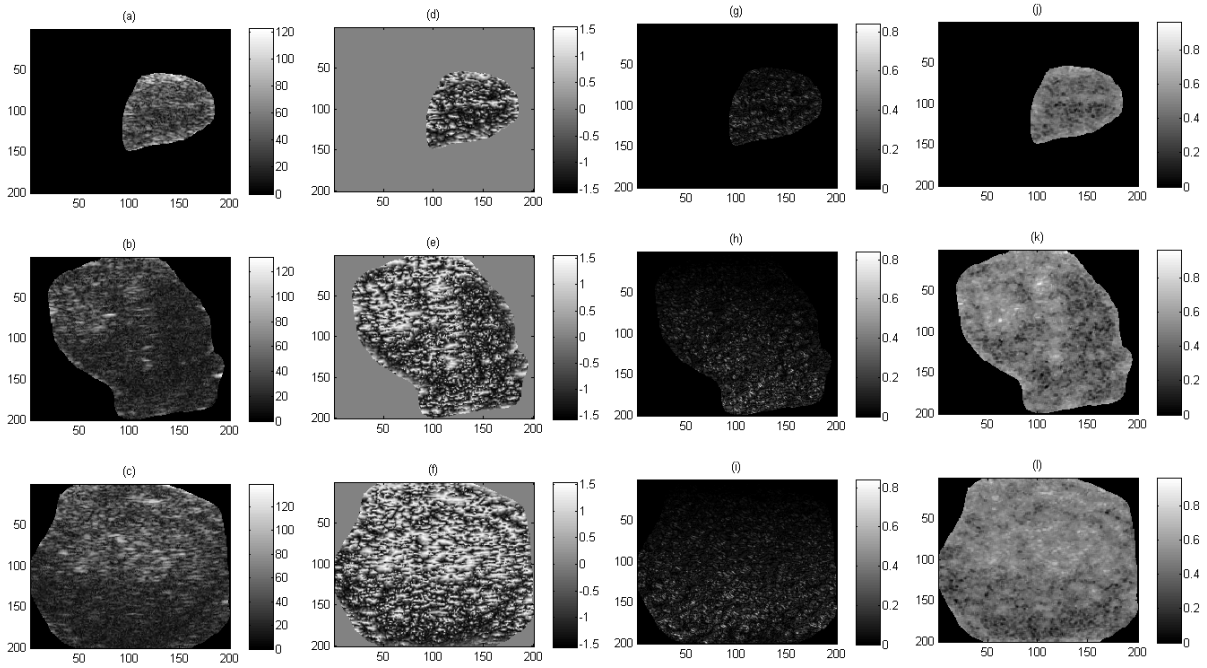

Figure 3. (a-c) Original 8 bit grayscale images images, (d-f) estimated local phases from a single scale, (g-i) uncertainties: higher uncertainties are shown in the location where no features (e.g. fibrotic structures) are present, (j-l) estimated significance map, higher values indicate fibrotic regions. For explanation of calculations refer to text.

local phases at each scale and image location should enable us to develop a local amplitude free method to estimate PC - this way overcoming the limitations of the current accepted Kovesi type PC. Future work should target to bring together the presented tools in a coherent probabilistic framework. Validation of the fibrotic regions with a larger dataset and histology is also needed - which is our future work.

Acknowledgements

We thank to Dr. Cat Kelly and Dr. Tine Mantoni for their helpful discussions on the experimental work. We would also like to thank to the anonymous reviewers for their suggestions.

A copy of the paper with the coloured version of the images is available on request from the first author.

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