A Spline Interpolation–based Data Reconstruction Technique for Estimation of Strain Time Constant in Ultrasound Poroelastography

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Abstract
Ultrasound poroelastography is a cost-effective and noninvasive imaging technique, which can be used to reconstruct mechanical parameters of tissues such as Young’s modulus, Poisson’s ratio, interstitial permeability, and vascular permeability. To estimate interstitial permeability and vascular permeability using poroelastography, accurate estimation of the strain time constant (TC) is required. This can be a challenging task due to the nonlinearity of the exponential strain curve and noise affecting the experimental data. Due to motion artifacts caused by the sonographer, animal/patient, and/or the environment, noise affecting some strain frames can be significantly higher than the strain signal. If these frames are used for the computation of the strain TC, the resulting TC estimate can be highly inaccurate, which, in turn, can cause high errors in the reconstructed mechanical parameters. In this paper, we introduce a cubic spline–based interpolation method, which allows to use only good quality strain frames (i.e., frames with sufficiently high signal-to-noise ratio [SNR]) to estimate the strain TC. Using finite element simulations, we demonstrate that the proposed interpolation method can improve the estimation accuracy of the strain TC by 46% with respect to the case where no interpolation and filtering are used and by 37% with respect to the case where the strain frames are Kalman filtered before TC estimation (at an SNR of 30 dB). We also prove the technical feasibility of the proposed technique using in vivo experimental data. While detecting the bad frames in both simulations and experiments, we assumed the lower limit SNR to be below 10 dB. Based on our results, the proposed technique may be of great help in applications relying on the accurate assessment of the temporal behavior of strain data.

Keywords
elastography, cancer imaging, frame reconstruction, cubic spline, time constant

Introduction
Ultrasound elastography is a noninvasive imaging method that can be used to assess the mechanical behavior of soft tissues based on the strains resulting from a small applied compression.1,2 Poroelastography is a branch of elastography, where the temporal mechanical behavior of tissues is assessed based on the spatial and temporal distributions of the strains resulting from an applied sustained compression.3–5 The temporal profile of the strains is related to the underlying fluid transport properties of the tissue, such as interstitial permeability and vascular permeability, while the steady state strains are linked to the linear elastic properties of the tissue, Young’s modulus and Poisson’s ratio. The strain time constant (TC) is an important poroelastographic parameter as it carries information on the fluid transport properties of the tissue.6–8 Fluid transport properties of tissues can be clinically very informative, especially in cancer applications.

In poroelastography, the strain TC is estimated from a series of temporal strain frames closely spaced in time to minimize decorrelation.9,10 However, in typical experimental conditions, many strain frames have signal-to-noise ratio (SNR) as low as <0 dB11 due to uncontrollable motion created by the operator, movement/breathing of the animal/patient, or the environment. The presence of these noisy frames can greatly affect accuracy of the strain TC.12

Typically, the strain TC is estimated using curve-fitting techniques. However, curve-fitting techniques have known limitations, especially if the underlying model requires fitting
a nonlinear function (as it is the case in poroelastography) since very small changes in the data can result in significantly different estimated parameters. Moreover, curve-fitting techniques are very sensitive to noise and can fail or reach an incorrect solution, if the data are characterized by low SNR.

A number of methods have been proposed to estimate the strain TC. The Levenberg-Marquardth (LM) is a popular method for strain TC estimation. However, this method is prone to error in noisy conditions. In the works of Sridhar et al., the authors used a traditional curve peeling/striping method first, and then fine-tuned the obtained estimates using a nonlinear Gauss-Newton fitting technique blended with the LM method. In another work, they estimated the strain TC and steady-state values searching poles and zeros in the Laplace domain. However, all these methods are modestly robust in noise and may fail to provide reasonable estimates in noisy experimental conditions. Recently, we proposed a curve-fitting method based on variable projection, which can estimate the strain TC from data with SNR as low as 30 dB. However, in many practical scenarios, the strain data be can of much lower quality (<0 dB). Thus, a method that can denoise the strain data prior the strain TC estimation could be very useful. In this paper, we propose a method based on cubic spline interpolation, which significantly improve the SNR of the temporal strain data. This method is used for prior estimation of the strain TC using curve-fitting techniques. We demonstrate that the use of this method can significantly improve quality of strain TC images.

**Problem Formulation**

In poroelastography, the first RF frame is the precompression frame and successive RF frames are postcompression frames at different time points under sustained compression. The axial strain between successive frames at a single pixel as a function of time can be expressed as

\[ x(t) = -\frac{\gamma}{\tau} e^{-\frac{t}{\tau}}, \]  

where \( \tau \) is the time constant of the exponential axial strain curve and \( \gamma \) is a constant parameter, which differs based on material properties and experimental protocol.

Integrating Equation (1) (equivalent to cumulative sum of discrete data), we get a generalized equation for the axial strain in a poroelastic sample during creep compression

\[ s(t) = \eta + \gamma e^{-\frac{t}{\tau}}, \]  

where \( s(t) \) is the axial strain temporal curve, \( \eta \) is the value of \( s \) at steady state (i.e., at \( t = \infty \)).

Since in practical experiments data are acquired discretely, Equation (1) can be written as

\[ x[n] = -\frac{\gamma}{\tau} e^{-\frac{nT_s}{\tau}}, \quad n = 1, \ldots, N, \]  

where \( T_s \) is the sampling time and \( N \) is the total number of time samples.

**Cubic Spline–based Frame Reconstruction**

Let us assume that among the available \( N \) data points, \( N_g \) data points are of high SNR and \( N - N_g \) are of low SNR according to a predefined quality standard. The essential idea behind the cubic spline–based data reconstruction is to fit a piecewise function of the form

\[ S(x) = \begin{cases}  
  s_1(x) & \text{if } x_1 \leq x < x_2 \\
  s_2(x) & \text{if } x_2 \leq x < x_3 \\
  \vdots & \\
  s_{N_g-1}(x) & \text{if } x_{N_g-1} \leq x < x_{N_g} 
\end{cases}, \]

where \( s_m \) is a third degree polynomial defined by

\[ s_m(x) = a_m (x - x_m)^3 + b_m (x - x_m)^2 + c_m (x - x_m) + d_m, \quad m = 1, \ldots, N_g - 1. \]  

The cubic spline needs to satisfy certain properties. First, the function \( S(x) \) will interpolate all data points. Second, \( S(x), S'(x), \) and \( S''(x) \) are continuous in the interval \([x_1, x_{N_g}]\). Using these two properties and the fact that the second derivative of \( S \) must be equal to zero at the end-points (\( x[1] \) and \( x[N] \)) for natural spline, the parameters to generate a unique cubic spline can be estimated. We refer to McKinley and Levine for further information on cubic spline–based interpolation.

**Methods**

**Spline Interpolation**

In spline interpolation, the spline polynomial equation (Equation 4) is fit to the known data points to obtain the coefficients. The equation is then used to estimate the function value at query data points. We used the least square error optimization technique (Levenberg-Marquardth) to find the equation coefficients and the mean square error as the cost function in the optimization procedure.

**Simulations**

A commercial finite element (FE) simulation software namely Abaqus (Dassault Systemes Simulia Corp., Providence, RI, USA), was used to simulate a cylindrical poroelastic sample containing a spherical inclusion under boundary conditions...
mimicking those of ultrasound elastography experiments. An instantaneous uniaxial stress of 1 kPa was applied on the sample for creep experiment simulation. The total analysis was recorded for 150 s in each step of 0.5 s. Please see the work of Islam et al.\textsuperscript{21} for a detailed description of the procedure used for poroelastic simulation of a cylindrical sample with spherical inclusion.

The sample specifications are given in Table 1. The sample size and mechanical properties were chosen based on previous work in the literature.\textsuperscript{22,23} The cylindrical sample has a radius of 2 cm and height of 4 cm. The inclusion has a radius of 0.75 cm. In all samples, the interstitial permeability was assumed to be $3.1 \times 10^{-14} \text{m}^4 \text{N}^{-1} \text{s}^{-1}$ in the inclusion and $6.4 \times 10^{-15} \text{m}^4 \text{N}^{-1} \text{s}^{-1}$ in the background region.\textsuperscript{22,23} The microfiltration coefficient was assumed to be $1.09 \times 10^{-6}$ (Pa s)$^{-1}$ in the inclusion and $4.44 \times 10^{-7}$ (Pa s)$^{-1}$ in the background region.\textsuperscript{22,23}

To create noisy strain data mimicking the ultrasound strain data, Gaussian noise was added to the strain data at different SNR (30, 40, and 60 dB).\textsuperscript{24} The SNR of the poor quality strain frames was set to 0 dB. The temporal positions of the noisy frames were selected randomly from a discrete uniform distribution of frame numbers in the range of 1 to $N$.

In this work, we considered ‘bad’ frames, all strain frames with an SNR of 10 dB or lower, the SNR being computed using the entire image. That is, strain frames with an overall SNR $<10$ dB are replaced using spline interpolation. The lesion is segmented based on known location (from FE simulations) in the noisy images.

The performance of the proposed method is compared with that of Kalman filter, which is often used to reduce noise in elastographic strain data.\textsuperscript{25} In the Kalman filter, the length of Kalman window was taken as 13.\textsuperscript{25}

Equation (2) is fit onto the noisy axial strain data and denoised strain data using the proposed method and Kalman filter by the curve-fitting tool in Matlab (Mathworks Inc., Natick, MA, USA) to estimate the strain TC.\textsuperscript{12} A least squared error minimization technique based on the LM method is used for the curve-fitting.

**Image quality analysis of the simulated data.** Quality of strain TC images was quantified using PRE (percent relative error). The PRE is defined as

$$\text{PRE} = \left( \frac{\rho_e - \rho_t}{\rho_t} \right) \times 100, \tag{5}$$

where $\rho_e$ is the mean estimated strain TC inside the sample and $\rho_t$ is the true parameter (from the ideal model shown in Table 1).

**Experiments**

The proposed spline interpolation method was tested on experimental data, acquired in a previous study. Details of the in vivo experiments have can be found in Islam et al.\textsuperscript{26} The experimental data were acquired in the context of a cancer animal study (Houston Methodist Research Institute, ACUC-approved protocol # AUP-0614-0033). As for the simulations, ‘bad’ frames were identified as those with SNR below 10 dB according to the method proposed by Chandrasekhar et al.\textsuperscript{27}

**Results**

**Simulations**

Figure 1 shows the final element method results obtained from noise-free data, noisy data of 60 dB SNR (no filtering, no interpolation), Kalman-filtered data, and spline-interpolated data, when 75% of the strain frames have high SNR. From this figure, we see that the exponential curves fitted to the noise-free and spline-interpolated data have TC values close to the ideal value (Table 1). On the other hand, the exponential curves could not be fitted to the noisy and Kalman-filtered data properly, and the TC estimates obtained from these data are far from the true value.

Figure 2 shows the resulting strain TC images using noisy, Kalman-filtered, and spline-interpolated data for data of 60 dB SNR for different percentages of good frames, that is, when the good frames are 75%, 50%, and 20% of the total number of frames. We see that, in most pixels, the strain TC estimates obtained from noisy and Kalman-filtered data are far from true value, and the resulting images are very noisy. The TC images obtained using spline-interpolated data have values closer to the true value (Table 2). As the percentage of good frames decreases, expectedly, the TC values obtained from the spline-interpolated data start to deviate from the

| Sample name | $E_i$ (kPa) | $\nu_i$ | $\tau_i$ (s) | $E_b$ (kPa) | $\nu_b$ | $\tau_b$ |
|-------------|-------------|---------|-------------|-------------|---------|---------|
| A           | 49.17       | 0.45    | 4.66        | 32.78       | 0.47    | 11.42   |
| B           | 97.02       | 0.45    | 2.36        | 32.78       | 0.47    | 11.42   |
| C           | 63.90       | 0.47    | 2.26        | 32.78       | 0.49    | 3.08    |

$E_i$, $\nu_i$, and $\tau_i$ Denote the Young's modulus, Poisson's ratio, and strain time constant, respectively. Subscripts $i$ and $b$ denote the Mechanical Parameters Corresponding to Inclusion (Tumor) and Background (Normal Tissue) Region.
true value as seen in Figure 2(c3). These observations are confirmed by the error images (computed as the difference between the true strain TC image and the estimated strain TC image), which are shown in Figure 3. From this figure, we see that the error associated to the strain TC estimated by the spline interpolation method is overall low (≈0 in most places) and significantly lower than those of noisy and Kalman-filtered data. The error increases as the percentage of good frames decreases. However, the error in case of spline-interpolated data does not increase significantly even when the number of good frames is only 20% of the total number of frames.

Similar scenario can be seen for the data at 30 dB SNR as shown in Figure 4 for different percentages of good frames, that is, 75%, 50%, and 20% of the total frame number. We see that, even in the case of 30 dB SNR, the strain TC estimates from spline-interpolated data have values close to the true value (Table 2). Overall, in the case of 30 dB SNR, the noise in the estimated strain TC images from noisy, Kalman-filtered, and spline-interpolated data increases when compared with the estimated strain TC images from data of 60 dB SNR.

The PRE in estimated strain TC images from noisy, Kalman-filtered, and spline-interpolated data at 60 dB SNR for sample A are shown in Table 2. From this table, we observe the highest error for noisy data and the lowest error for spline-interpolated data. The error can be as high as 55.26% in case of noisy data at 30 dB SNR with 20% of total frame being of high SNR, whereas the PRE in estimated strain by the proposed method is 8.17% and by Kalman filter is 45.11%. For the spline-interpolated data, the error can be as low as 5.61% at 60 dB SNR when 75% of the frames are of high SNR, whereas the PRE in estimated TC from noisy data is 32.05% and from Kalman-filtered data 28.31%. Overall, PRE reduces for all the methods, when the percentage of high SNR frames increases.

The computed errors in samples B and C are shown in Table 3 and 4. Overall, the error increases at all SNRs in sample C and decreases in sample B when compared with sample A. This may be because of higher Young’s modulus contrast in sample B and lower TC contrast in sample C.

**Experiments**

The B-mode image corresponding to a mouse tumor is shown in Figure 5 (a). The associated strain TC images are shown in (a2)-(a2) from noisy, Kalman-filtered, and spline-interpolated
From these figures, we see that, in the presence of high noise (Figure 5 (a2)) and without the use of interpolation, the curve-fitting method (LM) fail to estimate the strain TC. However, after the proposed spline interpolation method is used, the SNR of the strain data improves, and LM can estimate the strain TC accurately as found in Figure 5 (c2).
low strain TC values inside the tumor and higher strain TC values at the normal tissue region estimated from spline-interpolated data (Figure 5 (c2)) correlate with results available in the literature.28

Discussion

In this paper, we propose a novel technique based on cubic spline interpolation for accurate estimation of strain TC from a series of temporal strain frames obtained in a poroelastography experiment. In practical poroelastography experiments, several strain frames may have low SNR. This affects accuracy of strain TC and steady state strain estimations. Strain TC and steady state strains are crucial for accurate estimation of tissue parameters such as Young's modulus and Poisson's ratio29 as well as vascular permeability.18 It should be noted that the strain TC estimation error is nonlinearly related to the strain SNR, that is, it increases nonlinearly as the SNR decreases as shown in our previous work.30 Our results show that the proposed method based on spline interpolation dramatically improves the SNR of the strain data and, thus, can be of great help when the strains are used to reconstruct tissue mechanical parameters.

In the current implementation of the proposed method, the good frames from the in vivo poroelastography experiment have been selected based on the work of Chandrasekhar et al.27

Figure 3. Error in estimated strain TC images (in second) at 60 dB SNR for (1) 75%, (2) 50%, and (3) 20% of total strain frames being of high SNR from (a) noisy strain data, (b) Kalman-filtered data, and (c) spline-interpolated data. TC = time constant; SNR = signal-to-noise ratio.
In the future, differentiation between ‘good’ and ‘bad’ frames can be performed using more advanced techniques such as statistical analysis, machine learning, and so on.

The computation time for the proposed technique is similar to that required for noisy strain TC estimation, which is significantly lower than that required for Kalman-filtered

**Figure 4.** Estimated strain TC images (in second) at 30 dB SNR for (1) 75%, (2) 50%, and (3) 20% of total strain frames being of high SNR from (a) noisy strain data, (b) Kalman-filtered data, and (c) spline-interpolated data. TC = time constant; SNR = signal-to-noise ratio.

**Table 3.** PRE (%) in Estimated TC at Different SNR Levels for Different PGF for Noisy, Kalman Filtered, and Spline Reconstructed Data in Sample B.

| PGF (%) | 20   | 50   | 75   |
|---------|------|------|------|
| SNR (dB) | 30  | 40  | 60  | 30  | 40  | 60  | 30  | 40  | 60  |
| Noisy   | 56.48| 54.93| 55.39| 58.13| 51.84| 55.05| 46.29| 41.18| 40.94|
| Kalman  | 47.04| 48.03| 45.77| 50.04| 49.10| 47.29| 45.39| 39.21| 37.84|
| Spline  | 9.64 | 9.43 | 9.11 | 8.83 | 7.98 | 7.53 | 7.18 | 7.02 | 6.53 |

PRE = percent relative error; TC = time constant; SNR = signal-to-noise ratio; PGF = percentage of good frames.
data. For a strain TC image of $128 \times 128$ pixel$^2$, the computation times required for noisy, spline-interpolated, and Kalman-filtered data are 451.6 s, 455.72 s, and 605.04 s, respectively. Further improvement in computation of the proposed method may be achieved by GPU (graphics processing unit) implementation and is left for future work.

In this work, we have chosen the cubic spline interpolation over other interpolation techniques for reconstructing the strain data for several reasons. First of all, the interpolation error of spline interpolation is lower than that of polynomial interpolation for the same order of polynomials. Second, the problem of Runge’s phenomenon does not arise in spline interpolation, in which oscillation can occur between points when high degree polynomials are used for interpolation.

Spline interpolation can result in inaccurate reconstruction, when the number of frames with poor SNR is very high (above 80% of the total number of frames). In such cases, application of the proposed technique may not useful. However, such cases are not typical in our experiments.

## Conclusion

In this paper, we propose a data reconstruction technique based on cubic spline interpolation to improve accuracy of strain TC estimation in ultrasound poroelastography applications. We

| PGF (%) | 20 | 50 | 75 |
|---------|----|----|----|
| SNR (dB) | 30 | 40 | 60 | 30 | 40 | 60 | 30 | 40 | 60 |
| Noisy | 49.47 | 41.95 | 38.98 | 35.32 | 34.90 | 34.77 | 32.28 | 32.07 | 26.39 |
| Kalman | 41.59 | 37.11 | 32.13 | 31.98 | 34.50 | 29.75 | 29.34 | 28.52 | 25.22 |
| Spline | 7.09 | 7.74 | 7.13 | 6.33 | 5.19 | 4.93 | 4.69 | 3.98 | 4.25 |

**PRE** = percent relative error; **TC** = time constant; **SNR** = signal-to-noise ratio; **PGF** = percentage of good frames.
demonstrate that the proposed method is robust to noise and can dramatically improve the quality of strain TC images. Availability of this method may impact quantitative cancer imaging methods as they typically require accurate strain TC estimations for the reconstruction of the tissue parameters.

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