

A model of tissue contraction during thermal ablation

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Abstract. A model of a globular protein is used to describe the contraction of tissue exposed to elevated temperatures. This will be useful in predicting the contraction of tissue that is observed during thermal ablation of tumours, which is a problem when trying to determine the ablation zone in post-operative images. The transitions between the states of the protein can be related to a change in the length of the molecule, which can be directly observed as a change in the length of the tissue. A three state model of a globular protein is used to describe the contraction of tissue exposed to elevated temperatures. A nonlinear fitting algorithm is considered here to fit available experimental data and thus to obtain the values of the model parameters. A sensitivity analysis of the proposed mathematical model is performed to determine the most important parameters in the model. The model parameters were obtained from experimental data of isothermal free shrinkage experiments. The predictions of the complete model show similar agreement with the data, well within the experimental error of 10 %. The overall activation energy and frequency factor were found to be 201 kJ mol^{-1} and $7.32 \times 10^{28} \text{ s}^{-1}$ respectively. The results show that the experimental data were well described by the three state model considered here. Furthermore, it was possible to determine the most sensitive parameters in the model. The model presented here will allow predictions of thermal ablation to be corrected for tissue shrinkage, thus improving mathematical simulations for treatment planning, although clinical translation will require adapting the model from experimentally obtained tendon data to soft tissue data.

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1. Introduction

Thermal ablation therapies are regularly used to treat tumours in a clinical setting. Microwave, radio-frequency and laser ablations are common thermal ablation techniques where cell death occurs as a result of exposure to elevated temperatures. The procedure results in tissue contraction, which is of concern in evaluating the outcome of the procedure using medical imaging, and in the validation of computational predictions of the ablation zone. Recently there has been a significant increase in the research conducted to quantify this effect (Brace *et al* 2010, Farina *et al* 2014, Rossmann *et al* 2014). *Ex vivo* experiments on bovine liver and lung have shown ablation zone contractions of up to 15 – 50 % in diameter and 25 – 75 % in volume (Brace *et al* 2010). These results suggest that measurements of the post-treatment ablation zone may underestimate the pre-treatment volume of tissue ablated. These observations suggest the need to consider the effects of tissue shrinkage when using mathematical simulations to predict post-treatment tissue ablation zone more accurately.

Tissue shrinkage during thermal ablation is a result of many interlinked complex effects, such as protein denaturation, contraction of collagen and dehydration; all known to occur at elevated temperatures (Daggett 2002). The underlying mechanisms of the individual and combined processes are not fully understood and has been an ongoing topic of research. Thermal denaturation of protein is a complex biological procedure where protein molecules in the nated state (helical structure) unfold to the denatured state (coiled structure). This process can be reversible or irreversible due to the unfolding and refolding observed in the different intermediate states.

Several experimental data for tissue shrinkage due to heating are available in the literature (Weir 1949, Chen *et al* 1997, Benjwal *et al* 2006). Most of these experiments can be categorised into two heating protocols: the temperature-jump and the controlled heating-rate. The former heats the specimen quickly to a target temperature and this is maintained at this temperature during the testing. It has the advantage of keeping temperature and time as independent variables. In the latter, the specimen is heated at a constant rate and the changes in length are recorded. This method has the advantage of reducing the number of specimens required.

Chen *et al* 1997 presented data from isothermal free-shrinkage tests (performed in the absence of mechanical loads) of bovine chordae tendineae subjected to elevated temperatures. Thermal denaturation of proteins results in an irreversible shrinkage of the tissue at a macroscale due to the unfolding of the proteins. However, one of the findings observed by Chen *et al* 1997 was the partial recovery of the shrinkage of the tissue when tissue subjected to an elevated temperature was returned back to baseline temperature of 310 K (37 °C). This recovery was also found to be dependent on the initial exposure temperature of the tissue.

Mathematical models have been developed to describe the heat-induced tissue contraction, based on an empirical approach or considering the kinetics of protein denaturation. In the former case, the tissue contraction at elevated temperatures were

considered to take an initial linear (or pre-transition) regime, a long-term linear (or post-transition) regime, and a nonlinear transition that occurs between the initial and the long-term regime (Chen *et al* 1998, Rossman *et al* 2014). The tissue recovery following heating was considered to take an exponential decay (Chen *et al* 1998). The latter case includes two-state models (Agah *et al* 1994, Dueck *et al* 2011, Qin *et al* 2014) with irreversible denaturation and three-state models (Lumry and Eyring 1954), which assumes that the denaturation process occurs in two steps: reversible unfolding of native protein and irreversible change of unfolded protein to the final denatured state. The two-state model is the simplest model available and has been frequently used for thermal shrinkage. However, due to its simplicity, it is unable to capture the partial recovery of the shrinkage observed by Chen *et al* 1997.

The aim of the study conducted here is to develop a mathematical framework for the behaviour of tissue contraction as a result of protein denaturation during thermal ablation. This is achieved using a three-state model with first order reaction kinetics describing the transition of molecules between various states, the values of the parameters involved to predict the contraction of tissue exposed to elevated temperatures and their respective sensitivities. It is the transition between different states that changes the length of the constituent molecules resulting in residual stress in the tissue and presenting as gross tissue contraction at the macroscale. This idea is not without precedent as previous research has shown that the contraction of tendon is a rate process involving a reaction of first order (Weir 1949). A three-state model is considered over the simpler two-state model as the latter is not able to capture the partial recovery of the tissue shrinkage observed by Chen *et al* 1997. This will allow predictions of thermal ablation to be corrected for shrinkage, improving their accuracy, and bringing treatment planning with mathematical models a step closer. Note that the model here does not attempt to disentangle the many complex processes arising during tissue contraction but rather group a lot of the complex effects into one simple and easily implementable model.

2. Methods

The mathematical model considered here is based on a consideration of the response of a globular protein to heating (Wright and Humphrey 2002). It assumes that there are only three states: native, N, unfolded, U, and denatured, D, thus grouping all the different intermediate states into one overall state. The reaction equation is thus:



where k_i are the reaction rates, which are assumed to be governed by the Arrhenius equation:

$$k(T) = Ae^{-\Delta E/(RT)} \quad (2)$$

where ΔE is the activation energy, R is the universal gas constant, T is the absolute temperature measured in Kelvin (K) and A is the frequency factor. The equations describing this system are thus:

$$\frac{dN}{dt} = -k_1N + k_3U, \quad \frac{dU}{dt} = k_1N - k_3U - k_2U, \quad \frac{dD}{dt} = k_2U \quad (3)$$

where $N + U + D = 1$. To determine the change in tissue length, a model to relate changes in protein state to length is needed. Assuming that the total length of tissue, L , is equal to the linear sum of the different states of the protein, this can be expressed as:

$$L = NL_N + UL_U + DL_D \quad (4)$$

where L_X is the total length of the tissue if all of the protein is in state X . This is a natural extension of a similar two-state model (Dueck *et al* 2011). The state variables $X \in \{N, U, D\}$ must then be interpreted as the proportion of protein in each state, $X = n_x/n_0$, where n_x is the number of proteins in state X and n_0 is the total number of proteins. For example, if all of the protein is in the native state then $L = NL_N = n_0L_N/n_0 = L_N$.

The experimental data from Chen *et al* 1997 are in the form of relative shrinkages as a function of time under isothermal conditions. The relative shrinkage is defined as:

$$\xi = \frac{L_0 - L}{L_0} = \frac{L_0 - NL_N - UL_U - DL_D}{L_0} \quad (5)$$

Assuming that initially all of the protein is in the native state, the relative shrinkage in (5) can be simplified to:

$$\xi = 1 - N - U\frac{L_U}{L_N} - D\frac{L_D}{L_N} \quad (6)$$

The proportion of proteins in each state and the length ratios, L_U/L_N and L_D/L_N , will thus affect the tissue length and thus the relative shrinkage of the tissue.

This model has introduced many more parameters than a simple mass kinetics model due to observations of the protein state being indirect and related instead to L . The full set of parameters is $\theta \in \{A_1, \Delta E_1, A_2, \Delta E_2, A_3, \Delta E_3, L_U/L_N, L_D/L_N\}$, which all need to be determined experimentally. Note that the length ratios are not expected to be functions of temperature, only the reaction rates.

To determine the parameters in the proposed model, data from isothermal free shrinkage on bovine chordae tendineae (Chen *et al* 1997) have been considered. These experiments record the change in length of the tissue samples, using a camera, when subjected to an elevation in temperature from the base temperature to a target temperature for a specific duration of time. This is followed by a return to the base temperature. Experimental data considered here were those tissue samples exposed to 343 K (70 °C), 348 K (75 °C), 353 K (80 °C) and 358 K (85 °C), in each case for a duration of 120 s followed by a return back to the base temperature of 310 K (37 °C).

The parameters in our model are determined using a nonlinear fitting algorithm and bounding the parameters such that their values were greater than zero. The proposed

Table 1. Values of the frequency factors, the activation energies and the length ratios calculated in our model.

Parameter	Value
A_1 (s^{-1})	3.68×10^{30}
A_2 (s^{-1})	5.68×10^3
A_3 (s^{-1})	2.85×10^5
ΔE_1 (kJ mol^{-1})	210
ΔE_2 (kJ mol^{-1})	38.6
ΔE_3 (kJ mol^{-1})	47.2
L_U/L_N	0.420
L_D/L_N	0.322

model is fitted to all four target temperatures using a Monte Carlo approach. Two hundred random initial parameter values are considered during the curve fitting process with the solution being the parameters with the best curve fit. A step function is considered at $t = 120$ s to introduce the change in temperature.

A sensitivity analysis is also performed on the model to determine the sensitivity of each of the parameters involved in the reaction rates. The motivation behind the sensitivity analysis was due to the wide range of parameter values available in the literature. The Morris method (Morris 1991), which is a global one-at-a-time sensitivity analysis method, is considered here to determine the sensitivity of each parameter involved in obtaining the reaction rates. The theory behind the Morris method is beyond the scope of this paper and thus is not included here. The basic outline of the Morris method in a similar context, however, can be found in Hall *et al* 2015.

3. Results

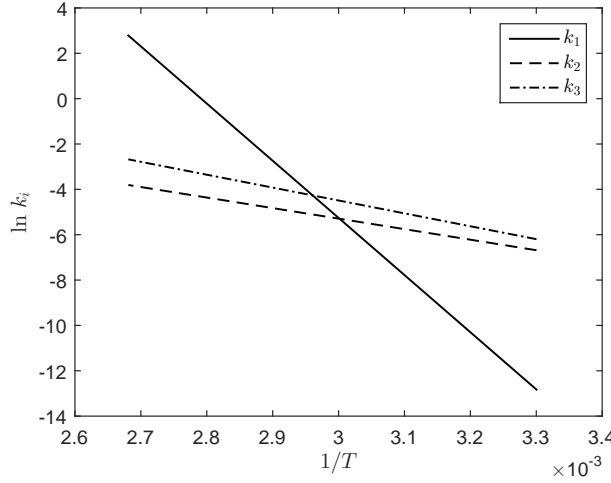
3.1. Tissue shrinkage

The parameters A and $\Delta E/R$ in the Arrhenius equation, (2), are constant with temperature being the only variable to obtain the reaction rate. The nonlinear fitting algorithm was thus applied to all four temperature data simultaneously. The parameters were bounded during the fitting to remove any possibility of arriving to a non-physiological set of solutions.

Table 1 shows the values of the frequency factor and the activation energy for the three reaction rates, and the length ratios obtained from the nonlinear fitting. The values of both the activation energy and frequency factor are largest for the forward reaction between N and U followed by the reverse reaction between N and U followed by the reaction between U and D. The results of the length ratios show that $L_N > L_U > L_D$ suggesting that the protein length is shortest when it is in the denatured state. Note that the parameter values obtained here is one set of possible solutions. Table 2 shows the root mean square error (RMSE) values for the parameters obtained. Note that the

Table 2. Values of the RMSE values for the curve fit.

T (K °C)	RMSE (%)
343 70	2.73
348 75	4.90
353 80	4.43
358 85	2.95

**Figure 1.** Variation of the reaction rates with temperature based on the Arrhenius equation.

RMSE values obtained here are smaller than the 10% experimental error described in Chen *et al* 1997.

Figure 1 shows the variation of the reaction rates with temperature (T) based on the Arrhenius equation. The different slopes of the reaction rates show that the response of the protein to heating will vary with temperature. For the parameter values obtained here, three distinct cases can be observed: (1) $T > 363$ K (90 °C), (2) $T < 303$ K (30 °C) and (3) 303 K (30 °C) $< T < 363$ K (90 °C). These values have been estimated from the plots and thus will depend on the values of the parameters determined during the curve fitting. For case (1) it is possible to approximate each state such that $N = 0$, $U = \exp(-k_3 t)$ and $D = 1 - \exp(-k_2 t)$. For case (2) it is possible to approximate each state such that $N = \exp(-k_1 k_2 t / k_3)$, $U = 0$ and $D = 1 - \exp(-k_1 k_2 t / k_3)$, where $k_1 k_2 / k_3$ is the overall reaction rate. This is equivalent to the two-state model. Case (3) exhibits the most complex behaviour between the three states since the similar magnitudes of the reaction rates leads to interaction.

The temperatures considered here lie within case (3) and thus complex behaviour of the three states is expected. $1/T$ varies from 2.79×10^{-3} K $^{-1}$ to 2.92×10^{-3} K $^{-1}$ where $k_1 > k_3 > k_2$. k_1 is generally an order of magnitude greater than k_3 , which in turn is an order of magnitude greater than k_2 . Thus at the target temperatures, the initial reversible thermal reaction between N and U is dominated by the forward reaction with

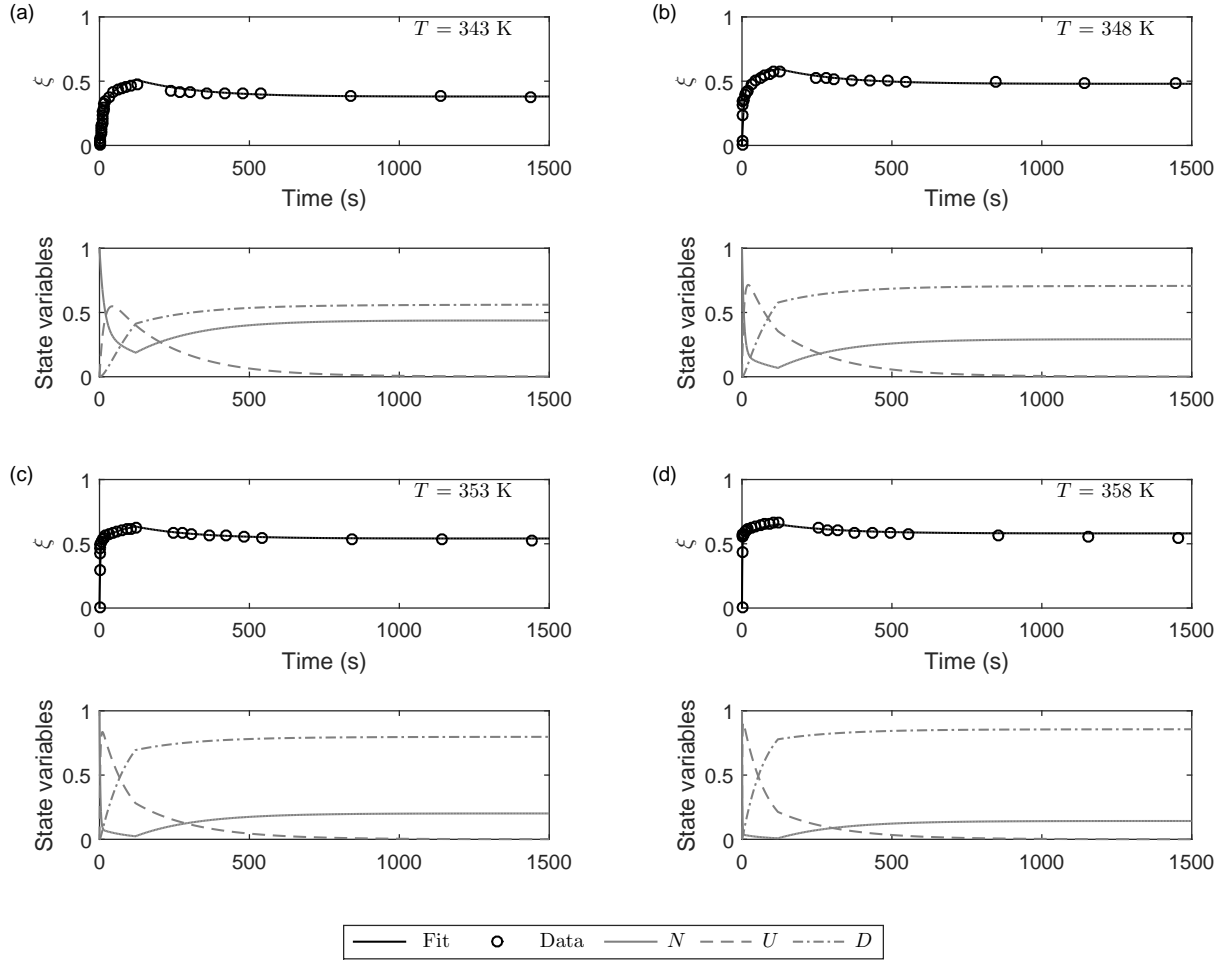


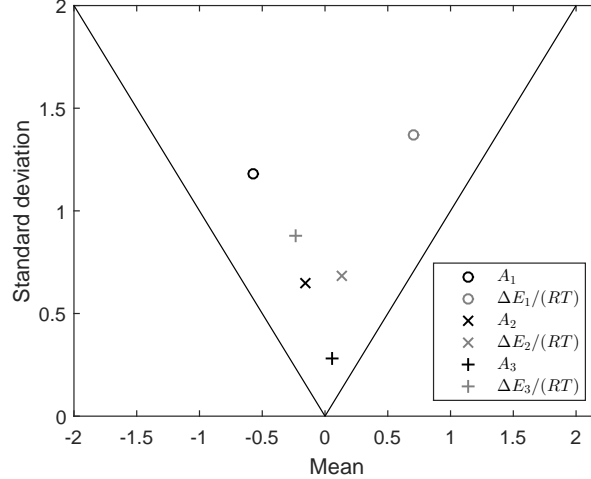
Figure 2. Plots of the relative shrinkage at the different target temperatures. The circle markers represent the experimental data whilst the solid line represents the fit obtained from the nonlinear algorithm.

the reaction between U and D being slowest.

Figure 2 shows the results of the nonlinear fit for the relative shrinkage data at each of the target temperatures considered and the proportion of protein in each state with time. Note that the temperature is returned back to the base temperature at $t = 120$ s. The plots at each temperature show a good fit to the shrinkage data, being able to capture the fast decrease in tissue length when exposed at the target temperature followed by the slower shrinkage rate and the recovery to a certain extent when the tissue is returned back to base temperature. The initial tissue shrinkage observed is due to the rapid change in protein state from N to U when the protein is heated to the target temperature and the relation of the total length with the proportion of proteins in each state. This is followed by the slower change in protein state from U to D . Since $L_U > L_D$, this change has a lesser effect in the decrease in tissue length as shown in the results.

Table 3. Range of values considered during the sensitivity analysis.

Parameter	Range
A_i (s^{-1})	5.1 – 75.0
$\Delta E_i/(RT)$	10.7 – 84.1
k_i (s^{-1})	$\mathcal{O}(10^{-35}) - \mathcal{O}(10^{27})$

**Figure 3.** Results of the Morris method when considering the protein state at the end of the simulation time.

When the tissue is returned back to base temperature, $k_3 > k_2 > k_1$. k_3 and k_2 are in the same order of magnitude whilst k_1 is an order of magnitude smaller. Hence the reverse reaction between N and U dominates the overall reaction followed by the reaction between U and D. The reverse reaction leads to the recovery in the tissue length and thus the drop in relative shrinkage. A higher target temperature leads to a higher proportion of tissue in the D state as the respective thermal reaction rates will be greater than when exposed to a lower target temperature, thus leading to an increase in the relative shrinkage.

3.2. Sensitivity Analysis

The Morris method was performed on our model with 100 random orientations and 6 parameters for a total of 600 numerical experiments. The temperature range considered was 50 – 100 °C, values that can be observed during ablation therapies (Brace *et al* 2010). The range of the parameter values considered here were obtained from the solutions during the nonlinear fitting where two hundred random initial parameter values were considered. The minimum and maximum values of both A_i and $\Delta E_i/(RT)$ from the two hundred solutions were chosen as the range for the sensitivity analysis and are shown in table 3. These values are within those reported in the literature (Qin *et al* 2014). The sensitivity analysis simulations were run for 1000 s.

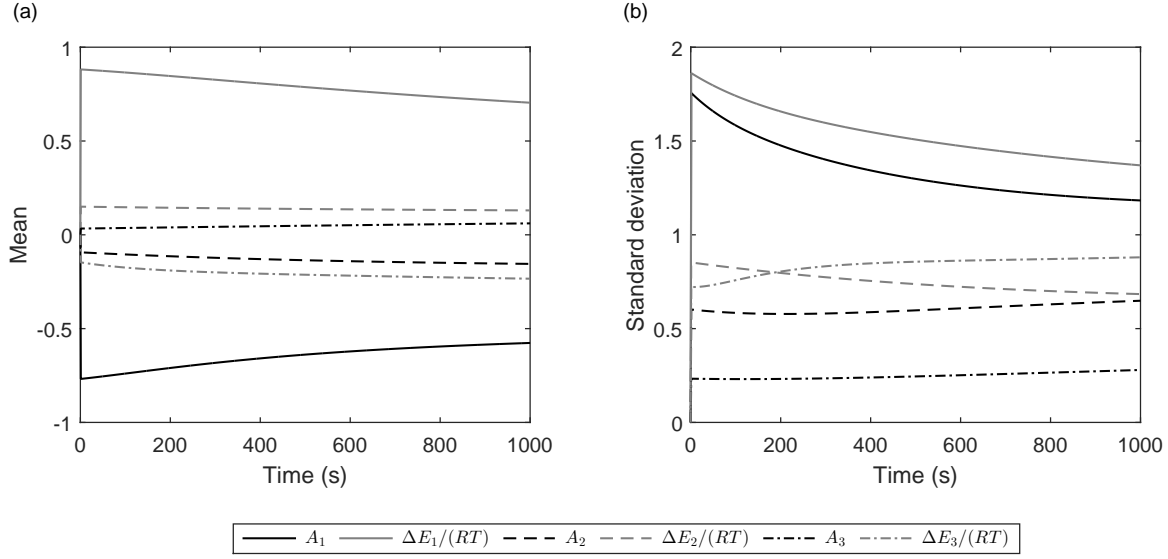


Figure 4. Sensitivity results of the Morris method. Mean and standard deviation of the each parameter is plotted over time to observe the change in sensitivity with time.

Figure 3 determines the overall influence of the output. The significantly smaller absolute mean value of A_3 relative to the other five parameters suggests a lower sensitivity to the output response. $\Delta E_1/(RT)$ and A_1 are clearly the two most sensitive parameters with the largest mean and standard deviation, and thus will have the greatest overall influence on the output. This is followed by the more clustered $\Delta E_2/(RT)$, A_2 and $\Delta E_3/(RT)$. All the parameters lie above the two lines, which represent when the magnitude of the standard deviation is equal to the mean. This suggests that either the individual effects are nonlinear or the interaction effects are significant in the output response.

Figure 4 shows the variation of the sensitivity measures with time. The results show that the order of the sensitivity of the parameters does not change with time and thus the output of the long-term exposure to elevated temperature is still greatly influenced by the parameters that determine the reaction rate from state N to U.

4. Discussion

The experimental data have allowed finding the values of the eight parameters involved in the tissue model. These were obtained by fitting all of the data simultaneously with the results showing that the shrinkage of bovine chordae tendineae, during exposure to elevated temperatures, can be well described by the model proposed here. It was necessary to interpolate the experimental values prior to fitting the data using a nonlinear algorithm to correct for the varying sampling rate of the experimental data. The interpolated data were obtained at equal intervals to remove any bias in the data. Furthermore, no temperature boundaries for state changes were introduced

as these were not known for the individual states. As a result, mathematically it was possible to determine reaction rates and thus changes in state even at temperatures where tissue contraction was not observed experimentally (< 50 °C). The shrinkage due to temperature can be directly related to the thermal expansion term in the linear elasticity equations providing a way of modelling the observed irreversible changes.

The overall reaction rate, k , for the three-state model proposed here can be obtained from:

$$k = \frac{k_1 k_2}{k_3} \quad (7)$$

Hence, the overall activation energy and frequency factor are $\Delta E = \Delta E_1 + \Delta E_2 - \Delta E_3 = 201$ kJ mol⁻¹, and $A = A_1 A_2 / A_3 = 7.32 \times 10^{28}$ s⁻¹ respectively. The values obtained here matched the empirical correlation of $\ln A = 0.3613\Delta E - 7.2511$ (ΔE measured in kJ mol⁻¹) obtained by Qin *et al* 2014 for proteins and are within the range of values available in the literature where the activation energy varies between 100 – 800 kJ mol⁻¹ and the frequency factor varies between $10^9 - 10^{129}$ s⁻¹.

The values of the parameters obtained here is one set of many other possible solutions that provide a good fit to the experimental data. Although the solution with the lowest error was used to obtain the values of the parameters, it is not possible to disregard other solutions due to the ± 10 % experimental error and the large number of parameters considered for the fitting. Knowledge of the length ratios could narrow down the possible solution sets significantly. To determine the effects of the uncertainties on the model parameters a sensitivity analysis was performed. The Morris method was considered as it determines the global sensitivity covering the entire space over with the parameters may vary. The results showed that $\Delta E_1/(RT)$ and A_1 were the two most sensitive terms to the overall influence on the output followed by $\Delta E_3/(RT)$, A_2 , $\Delta E_2/(RT)$ and A_3 . Furthermore, the greater standard deviation compared to the absolute mean suggests that either the individual effects are nonlinear or interaction effects that will dominate the output response (Morris 1991). The temperature range was chosen so that it would cause tissue contraction, above 50 °C (Brace *et al* 2010, Wright and Humphrey 2002), but keeping the effects of dehydration at a minimum. These effects become significant at temperatures close to and above 100 °C and thus the temperature was limited to values below 100 °C.

There are several other limitations to the proposed model. The complex chemical process of protein folding and unfolding were not considered here (Daggett 2006, Daggett 2002). The different proteins and their respective intermediate stages during the thermal denaturing process were simplified to follow the same behaviour with a single intermediate state. The model here only considers thermal denaturation. There are many other denaturants that affect the denaturation kinetics, such as pH, pressure and chemical agents.

So far a model of tissue contraction has been proposed that can be compared to experiments that measure the relative shrinkage of tissue exposed to elevated temperatures. In order to translate this study for clinical applications, it will require

coupling the model considered here with the equations of linear elasticity and the thermal expansion term in tissue. This term is an isotropic strain and can be expressed in terms of the relative shrinkage as:

$$\xi = - \int_{T_{ref}}^T \alpha dT \quad (8)$$

where α is the coefficient of thermal expansion, T_{ref} is a reference baseline temperature. During thermal ablation the tissue experiences a temperature that has both spatial and time dependence. In order to simplify the determining equations it is assumed that the temperature is evolving at a much slower rate than the tissue response. The displacement field resulting from elevated temperatures can therefore be considered to be extremely in equilibrium at all times.

In order to translate tissue contraction models to clinical thermal ablation therapies, it is necessary to know the composition of the tissue being considered. Differences in tissue composition will lead to different contraction rates due to varying overall mechanical properties. *Ex vivo* experiments on bovine pericardium (Chen *et al* 1997) and porcine liver (Rossmann *et al* 2014) have shown similar qualitative results with a rapid contraction of the tissue in the first 2 minutes. However, quantitatively the tissue contractions at similar target temperatures in bovine pericardium were found to be around three times greater than those observed in porcine liver. Other effects observed during thermal ablation, such as dehydration or charring, will also have different contributions to the total tissue contraction. For example, liver tissue is composed of over 70 % of water and thus the effects of dehydration will be more significant than other tissues with lower water contents. Levels of dehydration and charring are temperature dependent effects (Brace *et al* 2010) and thus more significant for microwave ablation therapies where tissue is exposed to temperatures up to 180 °C (Liu and Brace 2014). It is therefore also important to understand the effects of the different ablation therapies on tissue properties and temperature distribution (Brace 2009, Hall *et al* 2014). Currently there are not enough experimental data to develop accurate models of such effects observed during thermal ablation on soft tissue. An integrated model accurately predicting tissue contraction during thermal ablation therapies in a clinical setting will become possible in future as more experimental data becomes available.

The temperature range considered here suggests that the current mathematical model is more applicable to ablation modalities such as radiofrequency ablation, laser ablation and feedback-controlled intensity ultrasound, where the ablation temperatures do not exceed 100 °C, rather than microwave ablation, where tissue temperatures exceed 100 °C. Physical processes such as dehydration and charring may become significant at temperatures close to and above 100 °C, thus requiring additional investigation.

5. Conclusion

The results show that the shrinkage of bovine chordae tendineae during exposure to elevated temperatures can be well described by the three-state model proposed here. For the target temperatures considered here, the activation energy was greatest for the forward reaction between N and U, followed by the reverse reaction between N and U, followed by the reaction between U and D. The results of the length ratios also show that $L_N > L_U > L_D$ and thus the tissue length is greatest in the N state. This shrinkage can be directly related to the thermal expansion term in the linear elasticity equations, providing a way of modelling the observed irreversible changes. The sensitivity analysis considered showed that $\Delta E_1/(RT)$ and A_1 were the two most sensitive parameters with the interaction effects in the model found to be dominant in the output response.

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