Real-Time Assessment of Mechanical Tissue Trauma in Surgery

James H. Chandler, *Member, IEEE*, Faisal Mushtaq, Benjamin Moxley-Wyles, Nicholas P. West, Gregory W. Taylor, and Peter R. Culmer*, *Member, IEEE*

***Abstract*—*Objective*: This work presents a method to assess and prevent tissue trauma in real-time during surgery. *Background*: Tissue trauma occurs routinely during laparoscopic surgery with potentially severe consequences. As such, it is crucial that a surgeon is able to regulate the pressure exerted by surgical instruments. We propose a novel method to assess the onset of tissue trauma by considering the mechanical response of tissue as it is loaded in real-time. *Methods*: We conducted a parametric study using a lab-based grasping model and differing load conditions. Mechanical stress-time data were analyzed to characterize the tissue response to grasps. Qualitative and quantitative histological analyses were performed to inspect damage characteristics of the tissue under different load conditions. These were correlated against the mechanical measures to identify the nature of trauma onset with respect to our predictive metric. *Results*: Results showed increasing tissue trauma with load and a strong correlation with the mechanical response of the tissue. Load rate and load history also showed a clear effect on tissue response. The proposed method for trauma assessment was effective in identifying damage. The metric can be normalized with respect to loading rate and history, making it feasible in the unconstrained environment of intraoperative surgery. *Significance*: This work demonstrates that tissue trauma can be predicted using mechanical measures in real-time. Applying this technique to laparoscopic tools has the potential to reduce unnecessary tissue trauma and its associated complications by indicating through user feedback or actively regulating the mechanical impact of surgical instruments.**

***Index Terms*—Laparoscopic surgery, mechanical properties of tissue, real-time assessment, tissue trauma.**

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J. H. Chandler is with the School of Mechanical Engineering, University of Leeds.

F. Mushtaq is with the School of Psychology, University of Leeds.

B. Moxley-Wyles is with the School of Medicine, University of Leeds, and the Brighton and Sussex Medical School, University of Sussex.

N. P. West is with Leeds Institute of Cancer & Pathology, Leeds Teaching Hospitals Trust.

G. W. Taylor is with Leeds Institute of Biomedical & Clinical Sciences, Leeds Teaching Hospitals Trust.

*P. R. Culmer is with the School of Mechanical Engineering, University of Leeds, Leeds LS2 9JT, West Yorkshre, UK (e-mail: p.r.culmer@leeds.ac.uk).

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I. Introduction

SURGICAL instruments designed for laparoscopic surgery are subject to the geometric constraints of access ports (3-30 mm) and must meet stringent sterilization and economic criteria. It is the aim of the instrument design to allow *safe* and *effective* manipulation of the internal organs while conducting a surgical procedure [1]. Surgical graspers are traditionally made of steel, making them much stiffer than the tissues they manipulate [2]. Substantial effort has been made to understand and optimise the profiles of the graspers in order to reduce stress concentrations on tissues while maintaining retraction efficacy (i.e. preventing slip) [1]–[5]. However, the use of standard tools still currently results in tissue damage [6]. Tang *et al* [7] reported errors resulting in tissue injury during laparoscopic cholecystectomies could be attributed to graspers in 66% of cases, with 13% of these due to excessive force [7]. Considering the above, it is evident that grasper performance is modulated by two key factors; (i) their design; and (ii) the way in which they apply load to tissue.

Commercially available graspers vary in design, for example, jaw geometry and material produce significant variability in the peak pressures applied to the tissue [2], [8]. The tooth profiling size and geometric form has been directly correlated with tissue damage and grip performance- larger triangular profiles typically induce the most damage but deliver good grip performance [4], [5]. These profiles deliver local stresses which vary with orientation, jaw angle and geometry (including the presence of teeth) and tissue positioning on the grasper face [2], [3], [9]. Assessment of the applied stresses and modelling of the tissue interaction have been the focus of numerous studies [10]–[12], central to improving and optimising grasper jaws to provide maximal grip under loading conditions that will avoid inducing trauma.

In combination with design changes to instruments, it remains crucial to regulate the loading exerted by instruments on the delicate internal tissues of the body. However, this is a non-trivial task; with two primary challenges. Firstly it is not well understood how to define a 'safe' loading region [5], secondly the use of surgical instrumentation without haptic feedback may make it more difficult for the surgeon to assess or regulate the pressure applied to the tissue in real time [13]. Heijnsdijk *et al* investigated the effects of pressure on tissue trauma and proposed that an optimal load envelope should be defined within which an instrument exerts sufficient pressure to avoid slippage without inducing trauma [5]. De *et al*. [11] described how factors

associated with tissue damage were influenced by the applied peak stress. It was suggested that identification of a stress threshold and a stress dose may be useful in limiting the likelihood of inducing damage during routine manipulation [11]. Other studies, [2], [5] have also looked at establishing suitable 'safe' load thresholds. However, using thresholding approaches in isolation neglects the mechanical response of the tissue. Nagel *et al*. used theoretical modelling approaches to show that cellular stiffening also plays an important in tissue damage [14]. This body of research demonstrates that while mechanical factors cause tissue trauma, they can also be used to predict its onset. A number of groups have developed instrumented laparoscopic graspers to provide force and position feedback, with notable approaches including tactile arrays integrated into the jaws [15] and load and position sensors mounted within the handle [12], [16]. In conjunction, the next generation of robotic surgical systems will likely include force sensors to provide the surgeon with intraoperative haptic feedback [17]. While this enables the surgeon to subjectively regulate the application of appropriate loading it remains highly dependent on operator experience.

Independent of grasper type, sensing implementation or surgical modality, it remains critical to develop methods to analyse tissue loading data and thus predict and prevent the onset of trauma. Implementation of such analyses must be robust to the variable characteristics of grasper use in surgery (e.g. frequent adjustment of grasper position and applied load), the need for real-time prediction (e.g. not reliant on post-hoc analysis) and consideration of the mechanical response of the tissue (such as load rate and history). We propose that tissue stiffening can be practically obtained from measurements taken during surgery and that these parameters can be used to help predict tissue damage in real-time during direct manual laparoscopic or robotic surgery.

This study reports the development, assessment and implications of this trauma prediction technique. Section II formally presents the technique together with the test methodology and analyses used to assess its efficacy. Results from the study are then presented in Section III, followed by a discussion of the technique's efficacy and practical implications in Section IV.

II. Methods

A. Development of a Predictive Metric

The aim of the proposed technique is to transform mechanical measures obtained from an instrumented grasper system into a metric predictive of tissue trauma. A key requirement of this metric is that it should be practically implementable using readily measured information from the grasper within the uncertain environment of a surgical procedure. Ultimately, this could then be used to produce a control signal to guide the surgeon, or surgical-robot control system, during interaction with tissue.

First, it is important to define the mechanical information which can be directly measured, and subsequently derived, from an instrumented grasper during interaction with tissue. In this work we consider the grasper position to be static with respect to the tissue, resulting in a single degree of freedom system in which movement is confined to the compressive movement applied by the grasper jaws to hold the tissue. In this configuration, the angular position of the grasper jaws and the jaw-tissue load are readily measured, as in [16]. It is then necessary to consider the dynamic conditions under which grasping occurs in surgery, significant variability can occur in the magnitude of stress applied to the tissue, the rate at which it is applied and the time history of this process on a particular region of tissue.

The mechanical response of tissue is a result of the mechanical properties of the tissue combined with the environmental loading characteristics discussed above. Thus the challenge is developing a measure which can be determined without dependency on the environment. It is well recognised that biological tissues have complex mechanical properties, defined by the tissue's cellular composition and state, which typically exhibit a non-linear viscoelastic response under compression [18], [19]. Tissue stiffening has been shown to be indicative of tissue trauma [14] but extracting this information in real-time from a non-linear response is challenging. Models of varying complexity have been used to parameterise tissue response under load, ranging from non-linear formulations [20] through to simple approximations such as elastic modulus [21]. However, such approaches are limited in this context because they must be applied *a posteriori* and require knowledge of tissue loading state (i.e. thickness and load history). Accordingly, based on development of our prior work [16], we propose the 'loading rate normalised stress rate', $\bar{\dot{\sigma}}$, as a potential trauma metric that can be both readily measured in real-time and is robust to application in surgery.

This metric is defined in (1), where the time derivative of the measured stress signal is normalised by the time derivative of the position signal. In this case the current measured stress and position points, $(\sigma_i,\ x_i)$ respectively, are discretely differentiated through comparison to recorded data n and m data points previously and the associated time between points, calculated as the number of data points multiplied by the sampling time step Δt.

$$\bar{\dot{\sigma}} = \frac{(\sigma_i - \sigma_{i-n})/n\Delta t}{(x_i - x_{i-m})/m\Delta t} \tag{1}$$

The metric considers the rate at which stress is increasing in the tissue and normalises this with respect to the loading rate (the speed at which the grasper jaws are closing). It is calculated with signals that are easily measured and processed continuously in real-time. These properties make $\bar{\dot{\sigma}}$ applicable across the full range of operating conditions, to deliver continuous online monitoring during a procedure. Our working hypothesis is that a simple thresholding technique can be used with this metric, in combination with an absolute stress limit threshold, to identify the onset of tissue trauma.

B. Experimental Assessment and Characterisation

1) Experimental Approach: An experimental study was developed to assess the efficacy of the proposed $\bar{\dot{\sigma}}$ trauma identification metric. In particular this was designed to a) assess if $\bar{\dot{\sigma}}$ positively correlates with tissue trauma, b) characterise the response of $\bar{\dot{\sigma}}$ varied loading factors appropriate to surgery (rate and history) and c) define a suitable thresholding technique for

trauma prevention. Central to this study is a need to obtain clinically relevant measures of tissue damage in conjunction with the ability to parametrically vary and control loading conditions in order to explore their impact.

To satisfy these objectives, our methodology is based on a parametric series of tests in which controlled grasps are applied to *ex vivo* tissues in laboratory conditions. Measures were obtained from mechanical and histological analysis of the grasped tissue and these were then characterised using statistical techniques.

2) Experimental Equipment: A test system was developed to apply mechanically controlled compressive 'grasps' to tissue samples representative of those incurred during surgical interventions. Key requirements were that the test system should apply compressive grasps where the loading rate, peak stress and 'hold time' are directly controlled and have the capacity to apply a maximum stress of 300 kPa, previously demonstrated to be at the upper limit of surgical practice [11]. In conjunction, the system must obtain precise measures of grasper jaw position and resultant load for subsequent analysis of the tissue's mechanical response.

The resultant system is detailed in Fig. 1 and uses a linear actuator (LCA 50-025-721F3, SMAC) to drive together two 'grasp plates' (representing the grasper jaws) and thus compressively strain a sample of target tissue. The grasp plates were rapid prototyped at 16 μm resolution (VeroClear-RGD810, Objet1000 Plus, Stratasys, USA) and their geometry is typical of grasper jaws used routinely in laparoscopic surgery, with a triangular profile of 1mm pitch and a projected surface area of 120 mm^2 [8]. A high precision compression-link load cell (LCM-703-25, Omega) and USB webcam were used to record compressive stress and visual tissue deformation respectively. Control and measurement of the system was undertaken using a real-time data acquisition device with a programmable Field Programmable Gate Array (FPGA) interface (myRIO, National Instruments, USA). The latter was used to record grasp-plate displacement from the 0.1 μm resolution linear encoder integrated into the linear actuator. Custom software was written (LabVIEW, National Instruments, USA) to control the actuator motion and hold its position once a pre-defined load threshold was reached. In conjunction, the program was used to record position and load data synchronously at 1 kHz.

3) Tissue Model and Preparation: While the trauma assessment technique presented here was not developed to be limited to a particular tissue type, in this work we focused on colonic tissue (large intestine) to assess the technique's feasibility. Grasping and manipulation of colonic tissue is involved in the majority of laparoscopic surgery and safe grasping remains paramount due to its delicate nature and the potential for catastrophic complications if excessive pressures are applied.

A porcine model was selected for the colon tissues since it provides similar characteristics and sizes to human colon [22]. The animals used were bred and sacrificed in accordance with UK Home Office regulations (Animals [Scientific Procedures] Act 1986). Porcine colon tissue samples were obtained within 2 hours of slaughter and stored in phosphate-buffered saline (PBS) prior to preparation. Samples were identified and dissected from the most distal section of the colon, each cut to achieve tube sections of approximately 50 mm in width. Each sample was then cleaned and stored in PBS prior to testing. Samples were mounted into the testing system using a plastic clamp between the inner (mucosa) and outer (serosa) walls (Fig. 1), thereby maintaining an intact cross-section for grasping, replicating the mechanics of a surgical grasp.

4) Experimental Methodology: A two-stage experimental protocol was defined to fulfil the goals outlined in Section II-B.1.

a) Investigating Tissue Trauma: Our first objective was to evaluate if the mechanical measure $\bar{\dot{\sigma}}$ is a sensitive measure for tissue trauma. To investigate this we used the controlled grasping system (see Section II.B.2) to perform single grasps on colon tissue samples over a range of loads between 50 and 300 kPa. These loads represent the average pressure found in commercial laparoscopic graspers with a 0 degree angle of incidence between the grasper and the tissue [2] and have been identified in previous work as a critical pressure range for tissue trauma [11]. Other research has identified even higher pressures and resultant trauma occurring in some grasp conditions/areas, for example at the tip of grasper jaws or tooth point [5]. Accordingly we would expect to observe increasing tissue trauma as applied load increases from 50-300 kPa and that this would be exacerbated further at loads exceeding this range.

We assessed six loads (50,100,150,200,250 and 300 kPa) and performed nine repeats for each condition. A fresh tissue sample was used for each repeat; each was first rinsed in PBS, mounted in the tissue holder and compressed at a loading rate of 6 mm/s until the target load was achieved. The system then maintained this position (i.e. imposed a fixed strain condition) for a 10 s duration, used to represent a typical grasp, based upon our prior work [16], before releasing the tissue at the same rate as it was loaded, as shown in Fig. 1. Each tissue sample was then processed for histological analysis (see Fig. 2) with a unique identifier for subsequent correlation with mechanical measures of normalised stress rate $\bar{\dot{\sigma}}$ ((1)) and normalised stress relaxation $\overline{\Delta\sigma}$ ((2)).

b) Effects of Grasping Application: A second phase of testing was designed to assess the effect of repetitive tissue loading and of varying the loading rate, common features of tissue grasping in a surgical environment, on the mechanical response. The test procedure was similar to that described above, with the exception that for each load condition we evaluated three load rates (2, 6 and 10 mm.s^{-1}) and performed 10 grasp cycles (see Fig. 1(b)). Grasp cycles used a 50% duty cycle of a 10 s grasp followed by 10s unloaded. This configuration produced a total of 18 unique experimental conditions, each of which had 9 repeats. Mechanical measures of normalised stress rate $\bar{\dot{\sigma}}$ ((1)) and normalised stress relaxation $\overline{\Delta\sigma}$ ((2)) were obtained for each unique load/load-rate condition and segmented into individual grasp repeats. The influence of repeated loading and load rate variation was assessed through comparisons of these normalised metrics.

5) Mechanical Response Analysis: The mechanical response of each grasp across the various test conditions

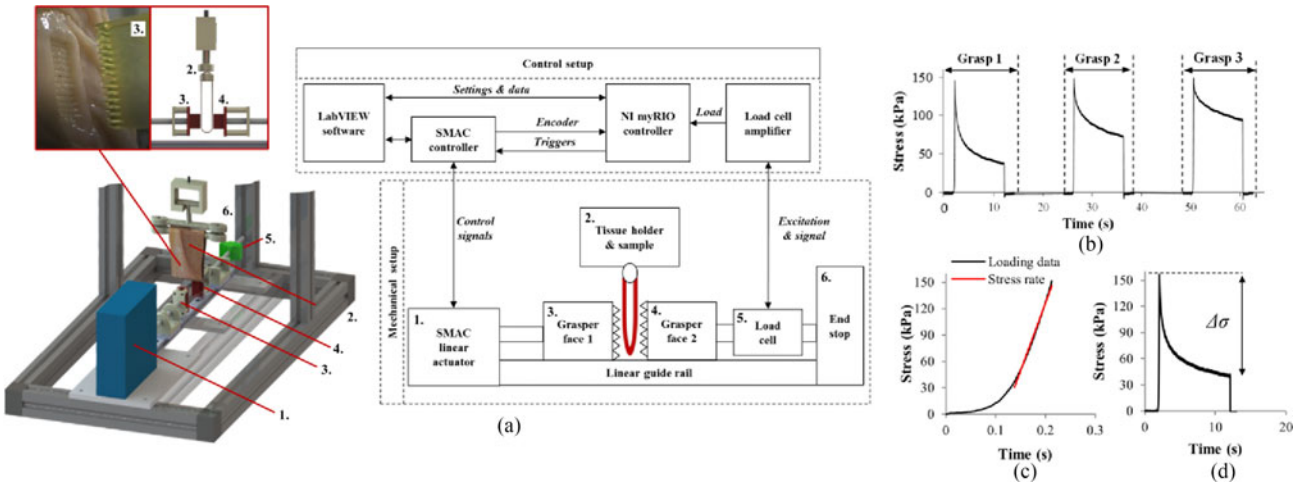

Fig. 1. Summary of the experimental testing setup with (a) schematic of testing equipment, (b) typical data, (c) stress rate metric, (d) relaxation metric.

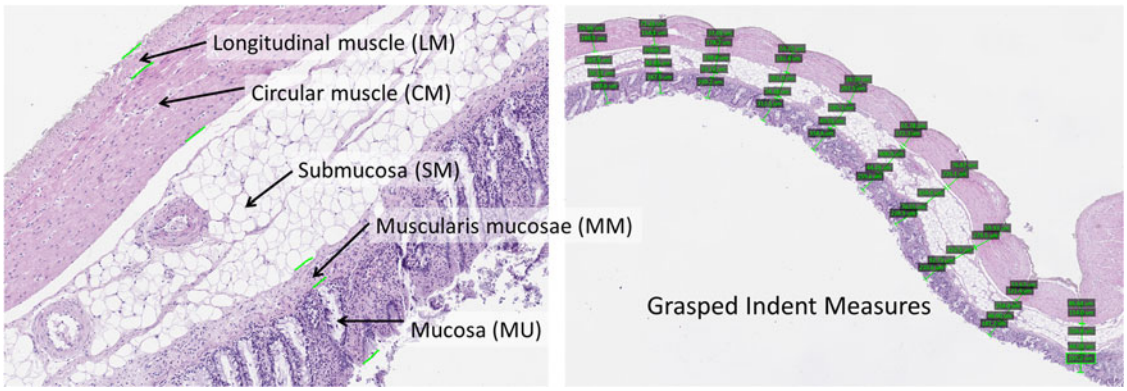

Fig. 2. Histological analysis: (left) constitutive layers of the colon and (right) quantitative measures of grasper indents.

described above was assessed through independent analysis of the loading and 'hold' phases, shown in Fig. 1(c) and (d) respectively. These were analysed to determine the normalised stress rate $\bar{\dot{\sigma}}$ ((1)) and normalised stress relaxation $\overline{\Delta\sigma}$ ((2)) respectively.

The loading phase (Fig. 1(c)) was defined as that from initial tissue contact up to maximal stress, $\sigma_{\max}$. A threshold for initial contact was defined computationally as being the first measured load point above five positive standard deviations from the arithmetic mean of the first 100 samples (0.1 s) of the load signal (before contact occurred).

Analysis of the load response was undertaken to investigate the characteristics of the normalised stress rate, $\bar{\dot{\sigma}}$, at the point of maximal stress, $\sigma_{\max}$. This was derived using linear regression analysis of the stress response between $\sigma_{(\max-n)}$ and $\sigma_{\max}$, a similar method to that used for elastic modulus determination [21]. Data were pre-processed using a low pass filter (second order Butterworth with a 50 Hz cut-off frequency) to attenuate high frequency noise from the measured signal. The number of data points included $(n+1)$ was increased until regression fitting accuracy fell below a fixed threshold $(R^2 < 0.995)$. The gradient of the final fit was taken as the value of $\dot{\sigma}$ and then normalised with respect to the applied loading rate to obtain the normalised stress rate metric, $\bar{\dot{\sigma}}$.

The hold phase (Fig. 1(d)) was defined as starting immediately after the load phase and continuing for a 10s duration. Stress relaxation is a physical feature that occurs when tissues are held under fixed strain due to the fluidic components in their cellular composition [23], [24]. Changes in stress relaxation are indicative of changes in the structural composition of the tissue [25] and thus provide an independent metric with which to characterise tissue damage.

The normalised stress relaxation, $\overline{\Delta\sigma}$, was defined as the reduction in stress during the hold phase, normalised by the peak stress of the grasp ((2)) and expressed as a percentage reduction.

$$\overline{\Delta\sigma} = (\Delta\sigma / \sigma_{\max}) \tag{2}$$

6) Quantitative Histological Analysis: Histological analysis was used to firstly understand how the tissue structure was affected as a result of mechanical loading and secondly to identify aspects of tissue trauma for correlation with the mechanical response measures. Histological analyses were performed to provide both a qualitative visual depiction of the

tissue composition and a quantitative description for statistical correlation.

Each tissue sample was processed following a timed protocol to help ensure consistent results. India Ink was applied to the grasper plate faces prior to each load test to allow for identification of the grasped region during processing and in the resultant histology slides. After the mechanical loading process each sample was removed from the experimental system and immediately stored in formaldehyde for 24 hours before being transferred to an ethanol solution (80% v/v %). Samples were then fixed and set in paraffin wax. Haematoxylin and eosin staining was performed following dewaxing and rehydration. Slides were obtained by slicing the tissue parallel with the row of grasper teeth (as illustrated in Fig. 3) and normal to the grasped surface, such that each constituent layer of the tissue could be observed. Three slides were obtained for each load condition, centred on the middle of the grasped area and spaced 1mm apart. Each slide was scanned (Aperio ScanScope XT2) at 200x magnification for subsequent analyses. From this set, a representative slide was selected based on image quality by a consultant gastrointestinal histopathologist to help mitigate against errors resulting from processing artefacts.

To quantitate changes in tissue structure, metrics were defined to represent the thickness of the constituent tissue layers within each sample. As illustrated in Fig. 2, colon tissue (both porcine and human) comprises five distinct layers enveloped within a thin serosa membrane; outermost and most proximal to the grasper teeth is the longitudinal muscle of the muscularis propria (LM), then circular muscle (CM), submucosa (SM), muscularis mucosae (MM) and finally the mucosa (MU) on the innermost surface adjacent to the colon lumen. Identification of these layers is important because their structural composition differs and consequently are likely to respond differently during loading. On each sample, the thickness of each tissue layer normal to the surface was assessed at 10 locations using a digital slide viewing platform (ImageScope v12, Aperio Technologies Inc.). Measures were obtained for loaded samples at each tooth 'point', the area of highest stress [26], where these could be identified. Three unloaded control samples were also assessed by taking measures at points equispaced across a 2 mm wide region. All measurements were performed by an experienced clinical histopathologist who was blinded to the loading conditions. In conjunction with the histological analyses, video was captured from the USB camera to examine the dynamic tissue behaviour during testing, providing further information for qualitative assessment.

7) Statistical Analysis: Statistical analyses were used to examine the effect of grasp pressure on tissue trauma and further to explore the characteristics of the different loading conditions. For each of the five tissue layers, separate one-way ANOVAs were conducted, with grasp pressure as a factor and layer thickness as the outcome variable. Thickness measures from normal tissues (i.e. ungrasped) served as a control. All of the variables were tested for normality to ensure the data met requirements for valid analysis of variance (ANOVA). Where data were not normally distributed, a transformation of the outcome variable was performed. When a significant difference was found ($\alpha = .05$) between the groups, post hoc Tukey's HSD comparisons were performed. Partial eta squared values (η_p^2) are reported to indicate effect size. To examine whether the mechanical response of tissue could predict damage, linear regression was conducted using the mechanical outcome measures: $\bar{\dot{\sigma}}$ and $\overline{\Delta\sigma}$ defined in Section II.B.5 with load increasing from 50 kPa to 300 kPa. All data were analysed using a combination of R (software version 3.1.3; R Core Development Team, 2015) and IBM SPSS version 20 (IBM, Armonk, NY).

III. Results

All testing was completed successfully and recorded in full by the experimental apparatus. Histology results were obtained for all load conditions and a representative slide with minimal processing artefacts was selected from each set.

A. Histological Results

A summary of the histology output across the six loading stresses is shown in Fig. 3.

1) Qualitative Histological Analysis: Qualitative observation of the stained sections suggests that immediately after grasping the applied load has caused concentrated areas of compression at the points of the grasper teeth rather than a uniform deformation along the width of the instrument. This pattern is reliably seen in stresses greater than 150 kPa. The area exposed to the grasper was clearly identified in all cases by the presence of India ink, however, tissue damage was hard to identify in some cases at a low loaded stress.

The majority of the tissue damage appeared to be within the outer longitudinal and inner circular layers of the muscularis propria with significant compression identified at the highest stresses. The stained smooth muscle fibres of the circular muscle (CM) layer in particular are seen to be more densely packed in the high pressure areas.

The submucosa appeared to show some evidence of compression, but only at the highest stresses. Occasional glands seen within the submucosa do not appear to have been disrupted. The muscularis mucosae and mucosa did not appear to show compression or trauma at any load stress and the glandular architecture has been protected.

2) Quantitative Histological Analysis: Quantitative outcome measures of individual layer thickness were obtained for the control samples and all loads with the exception of the lowest load condition (50 kPa) in which measures could not be reliably obtained. The normalised tissue layer thickness is indicative of the level of sustained tissue compression caused by structural alterations. For this study we therefore used layer thickness as an indication of tissue trauma. A graphical summary of the tissue layer thicknesses measured post compression is presented in Fig. 4.

For the Longitudinal Muscle, we found significant effect of pressure on muscle thickness ($F(5, 127) = 22.3$, $p < .001$, $\eta_p^2 = .47$). The impact of the applied loading for all stress levels significantly reduced tissue thickness relative to the control tissue sample ($M = 181.53$, $SE = 12.82$;

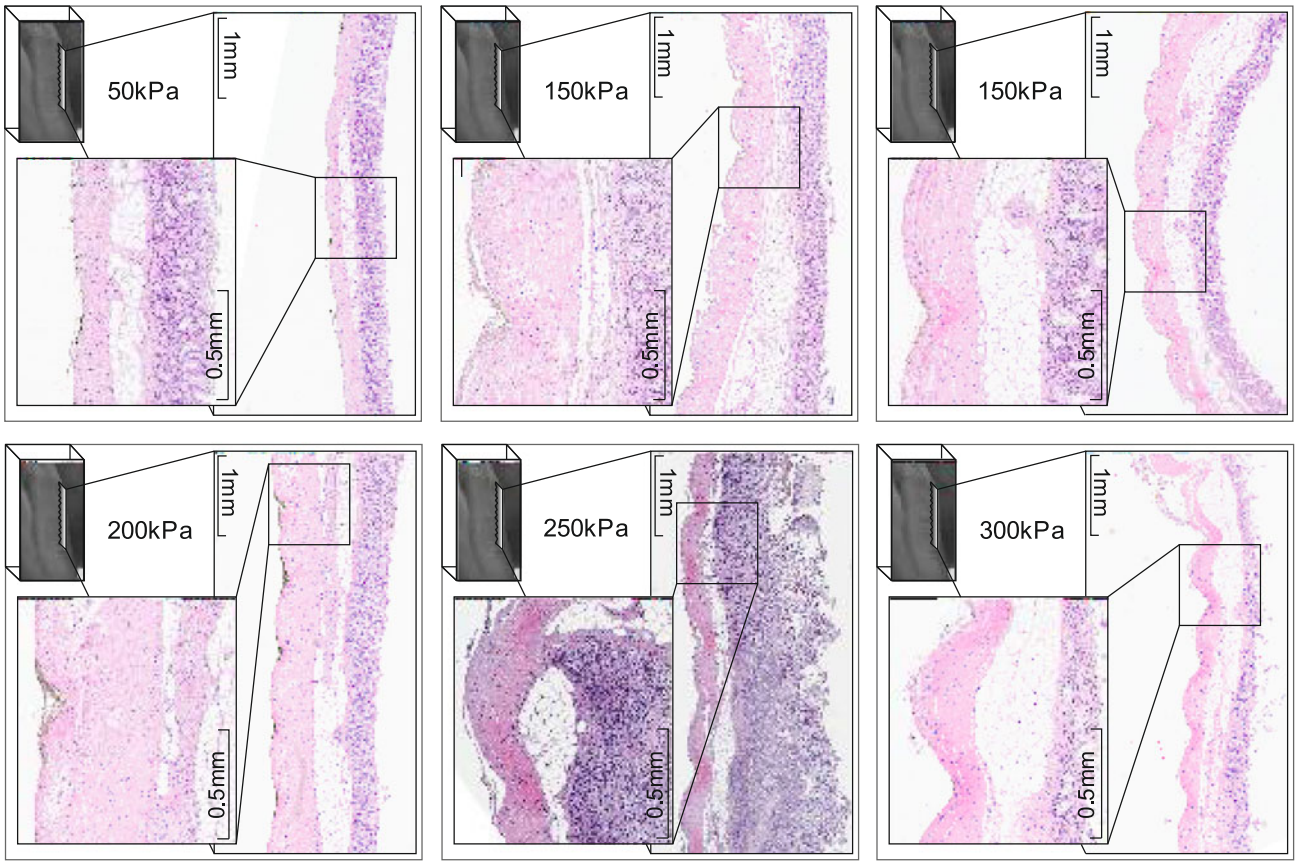

Fig. 3. Histological slides showing tissue structure after compression at each stress condition.

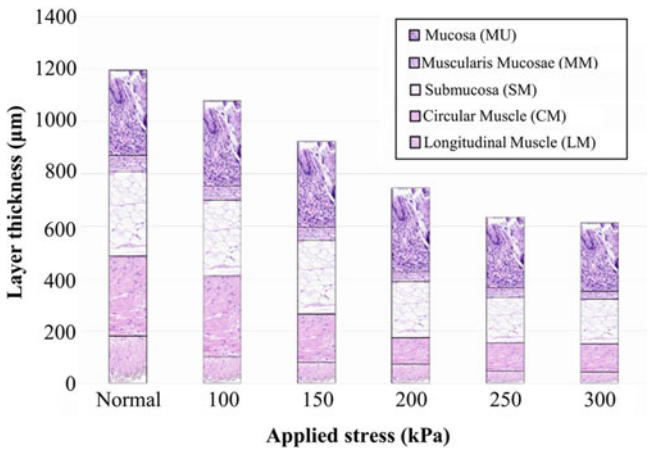

Fig. 4. Thickness of the colon tissue layers across the different load conditions as obtained through quantitative histological analysis. Shading of each layer is for illustrative purposes, taken from a single unloaded specimen.

p's $<$ .001). There was no difference in grasps of 250 kPa ($M = 45.44$, $SE = 7.02$) & 300 kPa ($M = 43.11$, $SE = 8.20$), but these two conditions produced lower tissue thickness scores relative to 100 kPa ($M = 102.81$, $SE = 9.33$; $p <$ .001), 150 kPa ($M = 81.09$, $SE = 7.54$; p's $<$ .011) and 200 kPa ($M = 74.76$, $SE = 7.14$; p's $<$ .048).

The Muscularis Mucosae also showed a significant effect of pressure on muscle thickness ($F(5, 115) = 12.34$, $p <$ .001, $\eta_p^2 = .35$). However, we found no difference ($p = .589$) between the lightest grasp (100 kPa; $M = 53.99$, $SE = 3.09$) and the control tissue ($M = 62.36$, $SE = 4.15$) samples. The control sample thickness was significantly greater than grasps at 150 kPa ($M = 47.13$, $SE = 2.48$, $p = .025$), 200 ($M = 38.84$, $SE = 2.53$, $p = .003$), 250 ($M = 33.93$, $SE = 2.4$, $p <$ .001) and 300 kPa ($M = 30.23$, $SE = 4.64$; p$<$ .001) conditions. The 100 kPa grasp had more muscle thickness relative to 200 kPa ($p = .003$), 250 kPa (p$<$ .001) and 300 kPa ($p = .001$). The mean thickness in the 150 kPa condition was significantly greater relative to 250 kPa ($p = .003$) and 300 kPa ($p = .021$).

There were no statistically significant differences for the 100 kPa sample relative to 150 kPa ($p = .515$) and control ($p = .589$). There were also no reliable differences for the 200 kPa when compared to 150 kPa ($p = .186$), 250 kPa ($p = .721$) and 300 kPa grasps ($p = .582$). The effect of pressure on thickness also appeared to reach a floor effect at 250 kPa-with no difference in pressure for this grasp relative to a stress of 300 kPa ($p = .981$).

For the Circular Muscle, there was also a significant effect of pressure on muscle thickness ($F(5, 109) = 61.44$, $p <$ .001, $\eta_p^2 = .74$). Similar to the Muscularis Mucosae, there was no significant difference ($p = 1.00$) between the control ($M = 304.43$, $SE = 14.36$) and the 100 kPa grasp

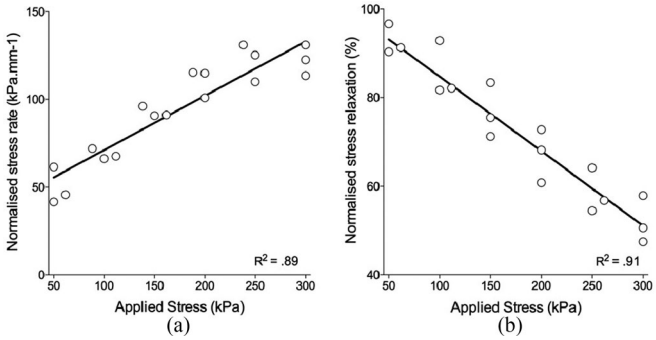

Fig. 5. Mechanical response of the tissue across the different load conditions showing (A) normalised stress rate during loading and (B) normalised stress relaxation during the hold phase.

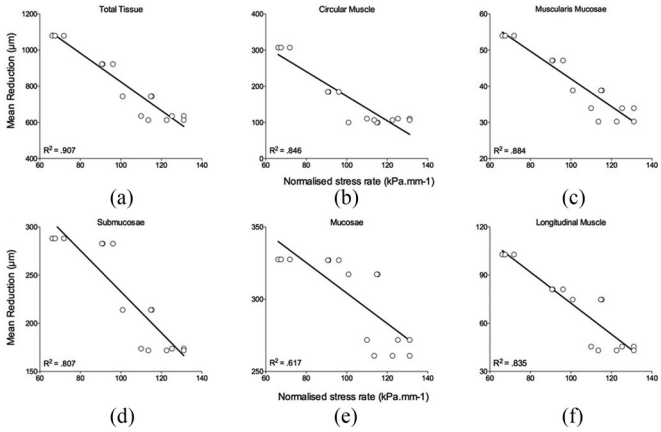

Fig. 6. The relationship between stress rate $\bar{\dot{\sigma}}$ and histological measures of tissue trauma.

(M = 307.06, SE = 14.36). However, the control was thicker than the tissue grasped with 150 kPa (M = 184.52, SE = 8.58, p < .001), 200 kPa (M = 99.59, SE = 11.72, p < .001), 250 kPa (M = 110.48, SE = 8.43, p < .001) and 300 kPa (M = 106.6, SE = 9.47, p < .001). Similarly, the 100 kPa thickness was significantly greater than all other grasped conditions (p's < .001). The 150 kPa grasp resulted in more muscle thickness compared to the 200 kPa, 250 kPa and 30 kPa grasps (p's < .001). However, there were no differences in the comparisons between grasps with applied stresses greater than 200 kPA (p's > .974).

The effect of pressure on the Submucosa thickness reached statistical significance ($F(5, 101) = 6.67$, p<.001, $\eta_p^2 = .25$). In post-hoc comparisons, we found no differences (p's > .117) in the control sample (M = 321.9, SE = 32.2) and grasps at 100 kPa (M = 288.15, SE = 29.39), 150 kPa (M = 282.76, SE = 19.6) and 200 kPa (M = 213.92, SE = 27.22). A difference compared to the control emerged only at grasps with forces of 250 kPa (M = 173.69, SE = 18.91; p = .002) and 300 kPa (M = 171.89, SE = 26.29; p = .006). This effect was mirrored in the measurements for 100 kPa and 150 kPa- where only the comparisons against 250 kPa (p's < .018) and 300 kPa (p's < .045) were reliably different. No other comparisons across grasps reached statistical significance (p's > .117).

Finally, for the Mucosa, we did not find a statistically significant effect of pressure on thickness ($F(5, 105) = 1.3$, p = .27, $\eta_p^2 = .06$).

B. Mechanical Outcome Measures

1) Effects of Pressure: Data from the first phase of testing showed strong relationship between our primary outcome measure ($\bar{\dot{\sigma}}$) and applied stress (Fig. 5(A)). Specifically, linear regression indicated that the normalised tissue stress rate $\bar{\dot{\sigma}}$ could be strongly predicted by the pressure applied (b = 1.860, $\beta = .941$, $t(17) = 11.147$, p < .001)- explaining 88.6% of the variance in ($R^2 = .886$, $F(1, 17) = 124.246$, p < .001).

The normalised stress relaxation $\overline{\Delta\sigma}$ was subjected to the same analyses. Similarly, pressure was a strong predictor of $\overline{\Delta\sigma}$ (b = −.168, $\beta = -.954$, $t(17) = -12.677$, p < .001), explaining 90.9% of the variance in impact on tissue ($R^2 = .909$, $F(1, 17) = 160.695$, p < .001). For each one increase in applied stress, there was a decrease by -.168 in $\overline{\Delta\sigma}$.

2) Mechanical Prediction of Tissue Trauma: Having demonstrated that quantitative histology and our real-time outcome measure ($\bar{\dot{\sigma}}$) each have a strong relationship with applied stress, we next investigated whether normalized stress rate could predict tissue trauma, as measured by our quantitative histological analysis. Fig. 6(A) shows the relationship between the total amount of tissue thickness and normalised stress rate (r = .952). A simple linear regression model is able to account for 90.7% of the variance in the total body of the tissue. Subsequently, we examined whether we could predict tissue thickness for each tissue layer. We found statistically significant linear models for each analysis (p's < .0005), but interestingly, the largest effects were observed for the outer muscle layers, with diminishing (but still relatively large) explanatory power towards the mucosa. These findings are entirely consistent with the pattern of results displayed in Fig. 4 where the outer layers, most proximal to the grasper teeth, are most impacted.

3) Effect of Varying Strain Rate: We examined the effect that varying loading rate and pressure had on the measured stress rate to investigate the behaviour of the tissue and also to validate the loading rate normalisation used in our predictive measure $\bar{\dot{\sigma}}$. A 3 (Loading Rate) X 5 (Pressure) mixed ANOVA revealed a significant Loading Rate X Pressure interaction ($F(10, 144) = 11.23$, $p < .001$, $\eta_p^2 = .44$). The results, shown in Fig. 7, demonstrate that the higher loading rates induce a higher stress rate response across all pressures, and more interestingly, that the response at low pressure for the high loading rate can exceed that of high-pressures at low loading rates. Thus, the data indicate that loading rate is likely to be a significant factor in tissue trauma.

4) Effect of Repeated Grasps: We next examined the tissue's stress rate response to repeated grasps (see Fig. 8). We fitted a one-phase exponential decay model for each grasp force ($Y = (Y_0 - Plateau)e^{(-KX)} + Plateau$) for the normalised stress rate (Fig. 8(A)) and normalised stress relaxation (Fig. 8(B)). Fig. 8(C) shows normalised stress rate collapsed across three loading rates (2, 6, 10 mm/s).

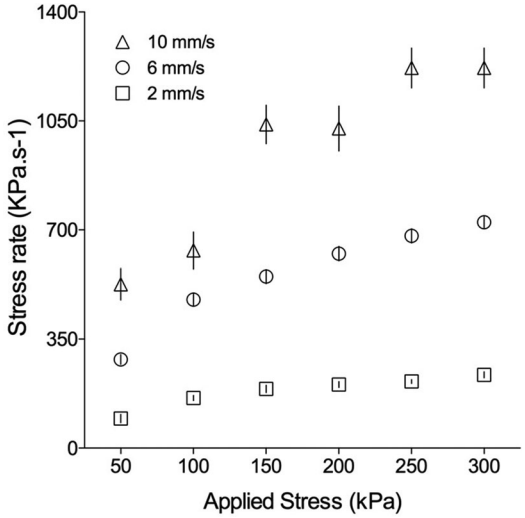

Fig. 7. Mechanical response (stress rate, $\dot{\sigma}$) of tissue at different strain rates.

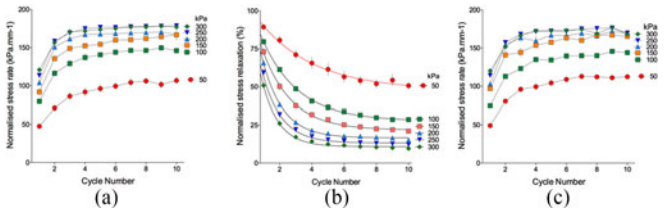

Fig. 8. Mechanical response of the tissue over repeated grasps for varied applied stress, showing: (A) normalised stress rate as a function of cycle number for a 6 $\mathrm{mm.s^{-1}}$ loading rate, (B) nomalised stress relaxation for the same test conditions as (A), (C) normalized stress rate as a function of cycle number for three loading rates (9 repeats at 2, 6, 10 $\mathrm{mm.s^{-1}}$ respectively, $\mathrm{n} = 27$).

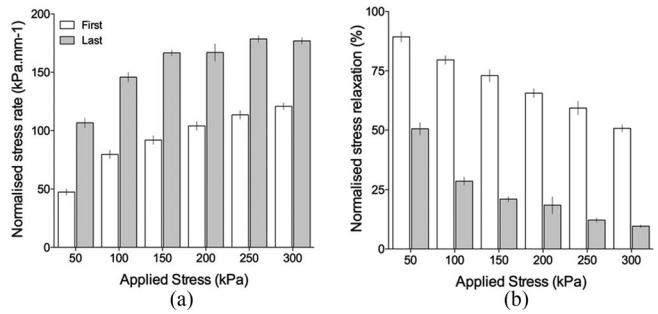

Fig. 9. Comparison of the tissue mechanical response between first and last grasps for normalized stress rate and relaxation.

Finally, we analysed whether there was a statistically significant difference in tissue mechanical response between the first and last grasp (Fig. 9) through a 2 (Grasp; First vs. Last) X Pressure (50-300 kPa) mixed ANOVA. For normalised stress rate $\bar{\dot{\sigma}}$, there was a large main effect of Grasp ($F(1, 48) = 1030.74$, $p < .001$, $\eta_{\mathrm{p}}^2 = .96$), but the Grasp X Pressure interaction did not reach the significance threshold ($F(5, 48) = 1.76$, $p < .001$, $\eta_{\mathrm{p}}^2 = .16$).

For normalised stress relaxation $\overline{\Delta\sigma}$, there was a Grasp X Pressure interaction ($F(5, 48) = 3.7, p = .007, \eta_{\mathrm{p}}^2 = .28$). This interaction was driven by the asymmetry in higher pressures. In the first grasp, there is a linear decrease, with significant differences across all comparisons (p's $< .048$). However, in the last grasp, normalised stress relaxation scores begin to converge across different pressures, such that at the end of these repeated grasps, there is no reliable difference between 100 kPa and 150 kPa ($\mathrm{p} = .162$), 150 kPa and 200 kPa ($\mathrm{p} = 1.0$), 200 kPa and 250 kPa ($\mathrm{p} = .508$) and no difference between 250 kPa and 300 kPa ($\mathrm{p} = 1.0$).

IV. Discussion

Histological analyses were central to this study- allowing us to identify the conditions under which tissue trauma may be likely and correlating these with our mechanical measures. Qualitative analysis revealed a clear correlation between increased pressure and the potential tissue trauma, indicated through sustained tissue compression. This showed trauma to be most likely at or above a threshold of 150 kPa, in agreement with previous studies [11]. The quantitative histological analysis enabled further investigation and it was notable that these characteristics were tissue layer dependent, whereby trauma was most probable at the muscle layers closest to the grasper teeth and entirely absent from the inner mucosa. Furthermore, different characteristics were apparent between the two muscle layers; the circular muscle layer are more densely packed in the high pressure areas. This may be a function of the direction of the applied grasp; as the grasper teeth in this study run parallel to the longitudinal muscle, the effect may have been to separate these fibres, rather than congest them, with the opposite true for the circular muscle fibres which run perpendicular to the direction of the grasper teeth. In contrast, the lack of damage to deeper layers may be due to the distribution of stress with increased depth (in agreement with computational models [26]) and the composition of the tissue, the loose collagen and elastin fibres that comprise the connective tissue may disperse the applied stress laterally, and are thus likely to recover more quickly than muscular layers. These differential characteristics merit further investigation. Alternative imaging techniques such as micro-ultrasound may help improve our understanding of how these tissue layers deform during grasping (as opposed to the post-grasp measures presented here) and have particular relevance to those considering atraumatic grasper design.

The qualitative histological analysis complemented and reinforced the quantitative analysis with clear differentiation of the magnitude of sustained tissue deformation observed across layers. Crucially, these data provided a means to statistically correlate observations of probable trauma with our mechanical measures. This is necessarily founded on the assumption that increased tissue deformation produces increased trauma, as found in this and other studies, e.g. [11], [26], [27]. A more direct measure would require assessment of living tissue in which the inflammatory response to grasping could be semi-quantitatively measured [11]. However, this is resource intensive and unsuited to the exploratory investigations reported in this study.

Establishing a quantitative definition of tissue response enabled us to evaluate our main hypothesis, that mechanical measures could predict tissue trauma. The strong correlations observed between our histological and mechanical loading measure show that, within the limitations of this study, $\bar{\dot{\sigma}}$ is a good predictor of resultant tissue trauma. The mechanical measures also provided a powerful tool to investigate the effect of load rate and grasp repetition on trauma. Tissue stiffness (indicated through stress rate) was found to increase with load rate, as shown in Fig. 7, in agreement with previous work [28]. This effect is likely to be a result of the high intracellular fluid content in these tissues (evident in the typically viscoelastic response during loading) and justifies the need to normalise our predictive metric in this respect. The normalized stress rate and relaxation (Fig. 8) also increased significantly with grasp repetition. Repeated grasps at low pressures at low pressures led to values of $\bar{\dot{\sigma}}$ that were higher than those of first grasps at higher pressures. This stiffening of the tissue may be due to migration of intracellular fluid with each grasp thus reducing protective 'cushioning' from the cells. This highlights the importance of grasp history on the potential for inducing tissue trauma and suggests the need for trauma predictive metrics based on a physical response, rather than relying on absolute stress thresholding alone. It also has real implications for clinical practice, suggesting that surgeons should avoid repeated manipulation of the same region which may increase the likelihood of incurring tissue damage.

There are practical considerations for the use of this metric in surgical instrumentation to prevent trauma. Firstly, the technique requires reliable real-time data of applied load and position of the grasper jaw, such that $\bar{\dot{\sigma}}$ can be calculated in real-time according to (1). Existing work shows that this is viable using a variety of approaches in both handheld laparoscopic instruments [12], [16] and robotic surgical systems where there is great interest in providing haptic feedback to the surgeon [17]. Secondly a thresholding method must be defined such that the continuous $\bar{\dot{\sigma}}$ measure is evaluated and related to tissue trauma. This measure is entirely complementary to using thresholding techniques on the applied tissue stress and to best identify tissue trauma it would be advisable to combine these measures. At its most basic, this may be a discrete assessment, 'safe' vs 'trauma'. For the colonic tissue used in this study a threshold can be defined by examining Figs. 3 and 4 to determine an applied load level associated with the onset of tissue trauma and subsequently correlating this to the $\bar{\dot{\sigma}}$ value of Fig. 5(A). For the case of applied stress values above 150 kPa being considered to show the potential for induced trauma, Fig. 5(A) would predict a normalised stress rate threshold of 100 KPa.mm^{-1}. Prior work into tissue damage thresholds suggest that this is likely to be tissue-type specific and a function of the underlying cellular structure [11]. The methods presented here could be used to characterise other tissue types and develop a valuable database of tissue trauma characteristics, including measures of applied stress and normalised stress rate. This would facilitate using such predictive techniques within routine surgery. Initially it may be necessary to manually define tissue types during use, but advances in multimodal sensing and analysis could help to automate this process and thus advance atraumatic surgical intervention.

The outcomes of this study are an encouraging step toward trauma prediction and prevention in surgery, but they are not definitive. It is worth noting that the interaction between the grasper jaws and tissue was limited to application of axial compressive stress. This represents a key aspect in grasping but it is recognised that trauma is also caused by shear stress (during tissue retraction), abrasion (when tissue slips) and jaw-tissue angle (manipulation of tissues) [2], [3], [9], [29]. Future work will consider these aspects to build a more complete picture of grasper-tissue interaction that can be practically applied in surgical settings to help prevent tissue trauma.

V. Conclusion

In this study we sought to better understand the mechanical behavior of tissue manipulated by graspers in surgery and in doing so develop a mechanical measure predictive of tissue trauma. Our parametric study demonstrated that histological analysis provided a valuable tool to characterise tissue trauma in qualitative and quantitative terms, and that it was possible to predict this trauma in real-time using readily obtained mechanical measures. The outcomes from this work have clear relevance to the 'end-user' clinical community and those scientists and engineers seeking to improve surgical instrumentation.

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Authors' photographs and biographies not available at the time of publication.