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14. ABSTRACT
This project aims to develop a platform for modeling of virtual tissues to be used in simulation of surgical and interventional procedures. The investigative team has made major advances in collection of mechanical tissue properties of the liver, integration into complex constitutive models, re-tooling the hemodynamic simulation model, and delivery of physics based visual models. Moreover, the group has been able to successfully demonstrate interaction of the virtual liver model with external forces including external shock wave and actual ballistic projectile. The results of the work performed during this award period have allowed for a physics-based model of tissue trauma and hemorrhage based on actual physical properties of the liver in a viscoelastic model, with superimposed hemorrhage using a smooth particle hydrodynamics method, in order to generate a high-fidelity virtual model of the said organ.

15. SUBJECT TERMS
liver constitutive modeling, material point methods, fluid/elastic multi-species continuum, hepatic tissue, hysteresis, compression, cardiovascular network simulation, hemorrhage modeling, smoothed-particle hydrodynamics

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INTRODUCTION:

The UCLA Center for Advanced Surgical and Interventional Technology (CASIT) shall lead an R&D program, "Virtual Tissue Modeling for Real-time Surgical and Interventional Procedure Simulation," to develop and evaluate a new virtual tissue modeling methodology for use in military medical training simulators for forward surgical and interventional care of combat injuries.

KEYWORDS:

liver constitutive modeling, material point methods, fluid/elastic multi-species continuum, hepatic tissue, hysteresis, compression, cardiovascular network simulation, hemorrhage modeling, smoothed-particle hydrodynamics

ACCOMPLISHMENTS:

- **What were the major goals of the project?**

The overall project goals are to develop a general framework for creation and sharing of virtual tissue models; create a prototype virtual tissue simulation of the liver and associated soft tissue and fluidic physiological systems; develop and integrate needed mathematical models, constitutive models, and interactive graphical models as a functional system of physics-based dynamic tissue simulations capable of real-time interaction appropriate for medical training simulators. The constitutive models shall be populated with validated physiological material properties. Virtual injury mechanisms and surgical tools shall be created for manipulation of the virtual tissue and methods developed for integrating component models (e.g. the liver) into a virtual patient body habitus model. Results shall be documented in a final report. The system shall be demonstrated in either a video or online interactive presentation format. The technologies and capabilities that shall be included are: computational simulation, graphical simulation, constitutive models, material property data acquisition, toolkits for injury and surgical procedures, and an online model repository and sharing system.

The goals for this reporting period were to continue research and development in the following focal areas:

1. Fluid dynamics & tissue constitutive modeling
2. Numerical methods for real-time modeling
3. Biomechanical and graphical modeling of organs
4. Tissue properties measurement and validation
5. Body habitus graphical and physical modeling
6. Medical requirements and assessment
7. Open standards development for virtual anatomic models
8. Project advisory activity

- **What was accomplished under these goals?**

1. Fluid dynamics & tissue constitutive modeling

There are two overall objectives of the fluid dynamics modeling team in this project. The first objective is to develop a comprehensive network model of the human cardiovascular system, with associated cardiac and autoregulation sub models, coupled with a fluid and nutrient transport model of the liver. The second major objective is to create a computational fluid dynamics simulation, based on smoothed particle hydrodynamics (SPH), of visualized bleeding from injury or surgical sites in the virtual model of the liver. These objectives are intertwined, since the visualized bleeding simulator requires the dynamic inflow conditions from the network model.

During this reporting period, we carried out a test on the full-scale liver model. In this test, the liver was subjected to a complete resection, carried out by applying a scalpel to the computational model that cut through the tissue. This resection cut through the outer layer and exposed the perfused tissue, allowing blood to drain. The complete set of tests can be seen here. The link is to a video submitted by our team to the Gallery of Fluid Motion at the American Physical Society's Division of Fluid Dynamics meeting.

We have also been carrying out an investigation of the use of data assimilation to improve fidelity of our cardiovascular modeling tool. In the previous term, we had used data assimilation to improve a limited cardiovascular model, of the pulmonary circulation. In this term, we began exploring the sensitivity of various common measurement modalities (e.g. brachial pressure, cardiac output) to variations in model parameters in the overall cardiovascular model. This sensitivity study provides essential information for determining what parameters can be tuned most effectively from measurement data. This process is carried out within an Ensemble Kalman Filter, which utilizes an ensemble of randomly-perturbed versions of the model. The mean of the ensemble results provides the prediction, and the spread of results provides an estimate of the uncertainty. Both are essential for constructing a modeling framework that can be applied on a patient-specific basis. In future work, this data assimilated cardiovascular model, in conjunction with the virtual tissue model, can be used to provide reliable simulations of liver injury and surgery.

We presented our work on both the virtual tissue modeling and on the data-assimilated cardiovascular modeling at the American Physical Society's Division of Fluid Dynamics meeting. We also have been preparing the virtual tissue modeling work for journal publication. This paper is nearly completed and will be submitted next quarter.

The sensitivity study of the cardiovascular model, started in the previous quarter, has been completed. We are also using the data assimilation framework for a different subtask now: determining optimal parameters for outlet impedance boundary conditions for CFD simulations. We are working with a CFD simulation of the lower leg for this task. Though it is not directly related to the virtual tissue modeling, it expands our capabilities for developing patient-specific models for biomedical simulation and training.

2. Numerical methods for real-time modeling

During This reporting period, the suture/strand model continues to resolve a good number of new phenomena, including simple contact and collision issues that we found were clearly an issue with our older approaches. We also made big strides in developing tissue failure visualization. Our discovery is a big improvement over the model we used in prior years.

We successfully submitted two papers related to our work on sutures/strands and ductile failure of soft tissues.

3. Biomechanical and graphical modeling of organs

During this reporting period, we worked on GPU cluster-based implementation. Computing the hyperelastic parameters is a more complex problem than estimating the linear elastic parameters. To this end, we need to employ a multi-GPU computing setup for estimating the hyperelasticity. We developed an innovative parallelization algorithm that use a multitude of search directions for the hyperelastic parameters. A set of 52 GPUs were employed in this study to analyze the hyperelasticity of each liver anatomy. The ground-truth deformation was calculated from the 4DMR datasets using an optical flow based deformable registration algorithm. The computation time for this step was approximately 2 minutes. Once estimated, each of the GPUs were then loaded with the same patient dataset and ground truth deformations. A central GPU was assigned the task of integrating the search results and disseminating the results to the other GPUs. Each GPU was assigned the task of optimizing a single hyperelastic parameters at a given time step. At the end of 5 search iterations, the results were then transferred to single CPU that sorted the hyperelastic values based on the observed cost/error. The value with the minimum cost is set and the search process continued with that hyperelastic parameters as the starting point. The process continued until the search process yielded a consistent result. To avoid being captured inside a local minimum, fast simulated annealing was employed by each of the GPU. The process randomly shuffles the search parameter based on an exponentially converging probability value. Results, showed that we were able to converge quickly on the estimated elasticity values.

We hypothesize that biomechanical modeling alone will be insufficient to characterize tissues for liver management. In future work, we will investigate the need to integrate tissue hyperelastic property estimation with blood modeling into an integrated model that will fully characterize the dynamic status of the patient's liver function. A critical component of this is the simultaneous automated vessel mapping using multiple FHFBCT scans. A goal of this aim is to provide vessel maps (tracheobronchial and bronchiole tree) that include vessels with sub-voxel cross sections. This is made possible by the quantitative nature of CT and the acquisition of numerous free-breathing images.

Reference Geometry: We first define a reference geometry, likely the geometry of the first MR scan. The selection of the specific reference condition is somewhat arbitrary except that it has to have unique spatial morphology and be able to be tied to the breathing amplitude and ultimately to the airflow model. The first helical CT scan meets both of these criteria.

We propose to take advantage of the quantitative nature of CT coupled with the multiple scan acquisition to map small bronchi and bronchi at sub-voxel resolutions. The justification for this is shown in Figure 7, where a bronchus has a sub-voxel diameter, but its impact on the voxel intensity can be measured as it transitions between two voxels.

Density-based subvoxel blood-vessel mapping: The voxel resolution of the FHFBCT scans are 1 x 1 x 1 mm^3, which corresponds to the diameter of the 6-10th bronchial generation. Further generations, such as bronchioles have sub-voxel diameters and might be considered to be undetectable (Figure 8). However, even sub-voxel bronchioles have an impact on the voxel density measurement. As the blood vessel moves between voxels, its impact on the MR voxel density can be predicted and mapped if there is a blood vessel tree (BT) map to guide vessel mapping.

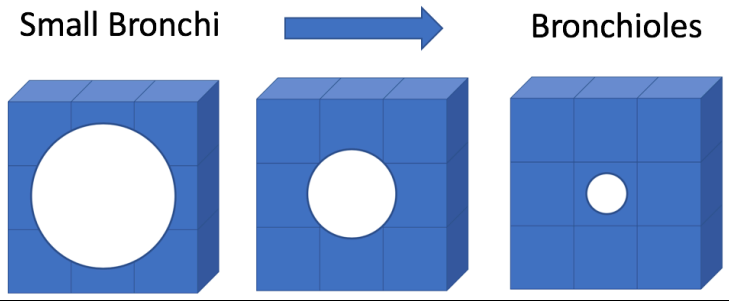

Fig 7. Schematic showing the partial volume averaging effect of imaging bronchi and bronchioles in CT.

Connectivity likelihood map using tubularity geometric features: Detecting the *potential* existence of a bronchus is insufficient to develop the vessel map. We also connect the BT using a technique we recently developed for imaging and tracking the small bowel. We propose to first generate a BT likelihood map over the imaged liver. Global geometric descriptors are challenging to identify the BT by themselves due to the variation of the BT shape between successive images. We propose to use both the global descriptor and density-based detection to characterize the chance of each pixel belonging to the BT. Our preliminary results of conducting this evaluation for the small bowel favored using a scale-optimized outward gradient flux, compared to alternatives such as Frangi or bi-Gaussian filter. Specifically, the flux at a specific scale σ is defined by

$$flux_\sigma(x) = \frac{-1}{4\pi r^2}\int_{S_r(x)} < \nabla(G_\sigma * I), \hat{n} > ds,$$

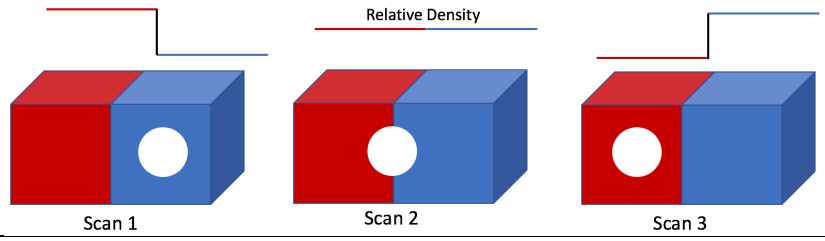

Fig 8. Schematic showing the impact of a sub-voxel bronchus on the MR-measured density for a series of MR scans that image the bronchus in different relative positions to the red and blue voxels.

where I denotes the image input, G_σ denotes a Gaussian kernel with bandwidth σ, $S_r(x)$ is the sphere with radius r centered on voxel x, and $\hat{n}$ is the outward normal on the sphere. To make the extracted flux feature robust towards the shape and scale variation in local sections of the BT, we propose to compute the flux at multiple scales, $\sigma \in \{\sigma_i\}, i = 1,,2, \dots, k$, normalize the computed flux at each scale, and use the maximum across the scales as the final flux characteristic value at each voxel, as shown below.

In previous studies, we found three scales of $\sigma \in \{2.0,3.0,,4.0\}$ to be sufficient. We further suppress parenchymal background using a function of voxel intensity. We calculate the probability that a bronchus resides within the voxel using a piecewise linear intensity map f

$$flux(x) = \max_{\{\sigma \in \sigma_i\}} flux_\sigma(x)$$

$$p(bronchus \in x) = c \cdot f(I(x)) \cdot flux(x)$$

Where c is a normalization factor to make the overall likelihood a legitimate probability, f is the intensity function kernel applied to the voxel-wise MRE image intensity, and $flux(x)$ is the scale-robust flux characteristic value.

4. Tissue properties measurement and validation

During this reporting period It is notable that all work on animal tissue with perfused liver models was completed and appropriate parameters extracted.

5. Body habitus graphical and physical modeling

During this reporting period, this group was integrated with the group, numerical methods for real-time modeling, working on modeling jointly.

6. Medical requirements and assessment

During this reporting period the goal was to continue ongoing evaluation of physiologic parameters in the present mathematical models. No additional animal experiments were planned at this time. Proof-of concept completion was completed with plan for prototype testing in the upcoming year.

Our goals were to complete analysis of preliminary results and finalize proof-of concept. We also continued discussions and preliminary mathematical modeling for additional physiologic parameters such as the respiratory cycle and intrathoracic pressure variation to current simulation. No other updates to provide from this quarter.

7. Open standards development for virtual anatomic models

During this reporting period, early major goals were as follows. Virtual liver models are essential in simulation platforms dealing with virtual surgery and training. The complexity inherent in the liver functionality, which stems from the blood flow as well as complex liver movements render the deformations to be high in computational complexity. Integrating the comprehensive model requires a novel approach to the open standards required for the medical simulation purposes. Conventional simulation platforms that support simulations with a generic computing setup (using Central Processing Unit) needs to be accommodated. Our focus is to develop a simplistic machine learning platform that can learn liver deformations.

Learning the open source liver model with hyperelastic parameters is a more complex problem than estimating the linear elastic parameters. To this end, we need to employ a multi-GPU computing setup for learning the hyperelastic liver model. We developed an innovative parallelization algorithm that use a multitude of search directions for the hyperelastic parameters. A set of 52 GPUs were employed in this study to analyze the hyperelasticity of each liver anatomy. The ground-truth deformation was calculated from the 4DMR datasets using an optical flow based deformable registration algorithm. The computation time for this step was approximately 2 minutes. Once estimated, each of the GPUs were then loaded with the same patient dataset and ground truth deformations. A central GPU was assigned the task of integrating the search results and disseminating the results to the other GPUs. Each GPU was assigned the task of learning a single hyperelastic liver deformation at a given time step. At the end of 5 search iterations, the results were then transferred to single CPU that sorted the hyperelastic values based on the observed cost/error. The value with the minimum cost is set and the search process continued with that hyperelastic parameters as the starting point. The process continued until the learning process yielded a consistent result. Results, showed that we

were able to converge quickly on the estimated liver deformation values. This enables a liver deformation hyperelastic model that enables open source liver deformations.

Additional major goals later in the year were as follows. Virtual liver models are essential in simulation platforms dealing with virtual surgery and training. The complexity inherent in the liver functionality, which stems from the blood flow as well as complex liver movements render the deformations to be high in computational complexity. Integrating the comprehensive model requires a novel approach to the open standards required for the medical simulation purposes. Conventional simulation platforms that support simulations with a generic computing setup (using Central Processing Unit) needs to be accommodated. Our focus is to develop a simplistic machine learning platform that can learn liver deformations.

We hypothesize that biomechanical modeling alone will be insufficient to characterize tissues for liver deformations. A goal of this aim is to also provide vessel maps that include vessels with sub-voxel cross sections. This is made possible by the quantitative nature of the imaging and the acquisition of numerous free-breathing images.

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Our initial results show that the open source liver model coupled with sub-voxel description of the liver blood vessel enables a high definition description of the liver deformations.

8. Project advisory activity

During this reporting period, this group has no new activity to report.

- **What opportunities for training and professional development has the project provided?**

Professional development and training was provided to the following individuals:

Graduate Student Researchers:

- Daniel Canuto (Mechanical and Aerospace Engineering)
- Yi-Jui Chang (Mechanical and Aerospace Engineering)
- Qi Guo (Mathematics)
- Michael Reyes (Mechanical and Aerospace Engineering)
- Ling Li (Electrical Engineering)
- Ashkan Maccabi (Bioengineering)
- Ahmad Abiri (Bioengineering)
- Tao Zhou (Computer Science)
- Xuchen Han (Mathematics, Computer Science)
- Mengyuan Ding (Mathematics, Computer Science)
- Stephanie Wang (Mathematics, Computer Science)

Postdoctoral Scholars:

- Dr. Kwitae Chong (Mechanical and Aerospace Engineering)
- Dr. Chenfanfu Jiang (Mathematics, Computer Science)
- Dr. Nathan Francis (Mechanical and Aerospace Engineering)
- Dr. George Saddik (Mechanical and Aerospace Engineering)
- Dr. Theodore Gast (Mathematics, Computer Science)

Surgical Resident Researchers:

- Yen-Yi Juo, M.D. (Surgery)
- Yas Sanaiha, M.D. (Surgery)

- **How were the results disseminated to communities of interest?**

For *Numerical Methods for Real-Time Modeling*, we primarily published in the computer graphics and computational physics literature. This includes the prestigious ACM SIGGRAPH and ACM SIGGRAPH Asia editions of the journal ACM Transactions on Graphics.

For *Biomechanical and Graphical Modeling of Organs,* we published numerous articles detailed below.

For *Medical Requirements and Assessment*, results were disseminated to fluid dynamics and the medical community through peer-reviewed publications and presentations and national conferences.

IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**

Summary: The team has successfully transitioned to GPU cluster based implementation of the computer simulations. We have employed a multi-GPU computing setup for computing higher level parameters such as hyperelasticity. Using such complex networks, we have been able to use 4D MRI datasets with an optical based deformation detection algorithm in order to determine tissue properties non-invasively.

It is notable that all work on animal tissue with perfused liver models was completed and appropriate parameters extracted.

The group has also been able to deconvolute the complex mechanical properties of a perfused liver that are essential in any physics-based simulation platform. Integrating such comprehensive model requires a novel approach to the open standards required for medial simulation at the present time. Our focus has been to develop machine learning algorithms that are less computationally heavy and can learn liver deformations. We have used the generalized Ogden material model as the base. We have used empirically derived stress-strain functions to tune the model. WE have now demonstrated the ability of the machine learning model to estimate deformation using a Green's function model and physics-based airflow distribution.

For *Numerical Methods for Real-Time Modeling*, we showed that machine learning is an effective tool for generating real-time simulation capabilities from large libraries of simulation data generated in offline, high-detail simulation. Furthermore, we developed a new simulation technique for simulating and visualizing soft-tissue injuries from projectiles and other blunt force trauma that drastically improve the state-of-the-art.

For *Biomechanical and Graphical Modeling of Organs,* liver deformation is essential for enabling a quantitative understanding of the liver and the overall lower abdomen physiology. However, liver deformation for normal physiological conditions is complex to model while they can be quantitatively observed in the 4D Magnetic Resonance Imaging. UCLA Radiation Oncology and Radiology employs 4D MR imaging for liver cancer radiotherapy treatments. Liver elastography is a critical component for enabling the liver deformation model. Liver diseases, such as liver cancer and cirrhosis, are commonly associated with changes in the biomechanical properties of liver tissue. Functional imaging techniques such as elastography have shown great promise in measuring the biomechanical properties of liver tissue; however, current liver elastography techniques require additional equipment that is conventionally not available within the radiotherapy setup. We present a novel methodology for estimating liver elasticity derived from deformation observed during 0.35 T 4DMR ViewRay (MRIdian System™, ViewRay™, Cleveland, OH, USA) scans within a radiotherapy setup. Phase 1 and phase 8 datasets, categorized by diaphragm position, were first deformably registered. The resulting displacement maps were considered ground-truth. A GPU-based biomechanical model was then assembled from the segmented phase 8 liver dataset and, along with patient-specific boundary constraints, used to iteratively solve for the liver elasticity distribution. The liver elastography process presented here was performed for a set of 11 4DMR patients. Maximum liver deformation was observed to be between 3.99 and 9.04 mm. On average, 95% convergence within 1 mm was observed. A validation study using phase 4 liver datasets illustrated an accuracy of 86%. Normalized cross-correlation quantified high similarity between the results of the estimation and validation studies with their respective ground-truths. Overall, the results suggest that liver elasticity can be measured with approximately 95% convergence using 4DMR scans acquired within the radiotherapy workflow, indicating the potential for the implementation of liver elastography within the clinic.

Liver deformations and modeling is a complex computational task that cannot be achieved in real-time using low-end computing platforms. A machine learning approach where the normal behavior of the liver undergoing breathing induced deformations is ideal for simulation and modeling applications, which forms the focus of this paper. In our approach, we employed a 4DMR image dataset acquired for liver cancer patients undergoing radiotherapy treatment. The individual liver volumes were registered using a multi-resolution optical flow platform to compute the liver deformations range. We then employed an adversarial network-based learning approach to learn the liver deformations for known elastic distributions obtained using model guided elastography. The neural network generated (a) liver elastography results, and (b) liver deformations for given liver geometry and stimulus representing the lung breathing phase. Results showed that using conventional low-end computing platforms, real-time liver deformations can be obtained in real-time.

For *Medical Requirements and Assessment*, the impact of this project on the development of theoretical multiscale models of biologic tissues has been tremendous. We have for the first time perfused a complex organ, the liver, with various pressures and measured its viscoelastic properties. Using complex algorithms, the group has been able to integrate such empiric parameters and produced highly realistic models for the bleeding liver.

- **What was the impact on other disciplines?**

For *Numerical Methods for Real-Time Modeling*, our algorithmic developments will be useful to the greater computational mechanics literature. In particular, we have developed new techniques for simulated porous liver filled with blood. These techniques can be used for general porous media. Furthermore, our novel techniques for simulating and visualizing ductile failure in the liver can be used for ductile failure of general materials. Lastly, our machine learning advances for simulating tissues in real-time can be used for a wide range of materials whose dynamics are not overly driven by inertia.

For *Biomechanical and Graphical Modeling of Organs,* other disciplines were impacted in the following ways:

Impact on Liver Imaging: In this paper, we presented the results of a liver elastography process performed on 11 4DMR datasets. A physics-based biomechanical model was used to solve the inverse elasticity problem. Liver DVFs from the registration of phase 1 and phase 8 diaphragm positions were obtained using an in-house optical flow DIR algorithm. Liver boundary displacements were employed as boundary constraints, while the inner liver tissue voxels were allowed to deform according to linear elastic material properties.

On average, 95% of voxels for 11 patients converged within 1.0 mm of ground-truth deformation. Maximum deformation ranged from 3.73 to 9.04 mm for the estimation cohort. The average elasticity ranged from 2.69 to 6.42 kPa. The average values found here correspond well with those found in the current work in the field (Singh, Venkatesh et al. 2015, Venkatesh, Yin et al. 2015, Zeng, Cai et al. 2017). In addition, an image similarity metric showed high similarity between the phase 8 and warped phase 1 registration and experimental results, with values of 0.97 and 0.97 respectively. Overall, these results suggest that liver elastography can be performed using ViewRay 4DMR datasets for a wide range of patients.

The potential of 4DMR liver elastography to be used in the clinic requires extensive validation. Phase 4 datasets were obtained as a validation cohort so that the elasticity results could be validated in a clinically-relevant manner. The maximum deformation ranged from 2.59 to 7.88 mm for the validation cohort, and 86% of voxels converging within 1 mm of clinical ground-truth deformation. An image similarity metric again showed high similarity between phase 4 and warped phase 1 registration and validation model results, with

values of 0.97 and 0.90 respectively. Future work will investigate obtaining MRE data for patients so the elasticity distributions can be more explicitly and quantitatively validated.

Impact on Liver Surgery/Radiotherapy: Hepatocellular carcinoma (HCC) is one of the most common malignancies, and the third most common cause of cancer-related death worldwide (Jung, Yoon et al. 2013, Jun, Kim et al. 2017). Surgical resection and liver transplantation are the primary treatment methodologies, however strict criteria limit the pool of eligible patients for both cases. HCC has a poor prognosis, with a 5-year survival rate of less than 12% due to a combination of late diagnosis and lack of efficient therapies for advanced stages (Affo, Yu et al. 2017). Stereotactic body radiotherapy (SBRT) has been used to treat patients with HCC who are not eligible for other treatments (Feng, Suresh et al. 2017). SBRT uses advances in imaging and conformal radiotherapy to deliver ablative, high dose radiation in order to optimize local control.

Radiation-induced liver disease (RILD) is a significant limiting factor in the use of SBRT because there are no effective treatments or predictors (Jung, Yoon et al. 2013). Most patients with HCC have pre-existing cirrhosis or hepatitis, which increases their risk of RILD (Kim, Kim et al. 2015). Baseline liver function is thought to be the most important factor associated with risk of RILD (Jun, Kim et al. 2017). Pre-treatment visualization of liver function in vivo is necessary in order to expand the use of SBRT for HCC.

The liver plays a role in metabolism, synthesis, secretion, immunity, and many other functions (Luna, Cunha et al. 2014). Liver disease, including cirrhosis, fibrosis and tumors, can disrupt the functions of the liver by altering the biomechanical properties of the tissue, most notably by changing the tissue stiffness (Sandrasegaran 2014, Li, Min et al. 2015). Clinically, elastography provides a measurement of liver stiffness and is a predictor for HCC (Pepin, Chen et al. 2014). Magnetic resonance elastography (MRE) can noninvasively and quantitatively assess the elasticity characteristics of soft tissue (Li, Min et al. 2015). Liver stiffness measured by MRE has been shown to correlate well with histologic staging of fibrosis and differentiation of benign and malignant liver lesions (Venkatesh, Yin et al. 2015). However, current MRE techniques require equipment that is not typically available within a radiotherapy setup.

Our elastography process focuses on estimating the effective Young's modulus for each voxel of liver tissue using 4DMR liver data. Figure 1 shows a flow chart summarizing the elasticity estimation. First, phase 1 and phase 8 datasets from the 4DMR liver images were registered using an optical flow deformable image registration (DIR) algorithm (Min, Neylon et al. 2014). Liver deformation vectors (DVFs) were obtained for every voxel of liver tissue. The biomechanical model was then assembled using segmented phase 1 liver geometry and a randomly initialized elasticity distribution. Using the ground-truth liver DVFs, the elasticity distribution was optimized. The inverse elasticity problem was formulated as a parameter-optimization problem with an objective to determine the elasticity parameter that would minimize the difference between the ground-truth deformation and the deformation computed by a biomechanical model. The biomechanical model and inverse elasticity estimation were implemented on a GPU cluster, which allowed the elasticity estimation for each patient dataset to converge in around 2 hours. Spatial elasticity and displacement error distributions were then obtained and validated.

Impact on Artificial Intelligence: The liver geometry was obtained from anonymized lung 4DMR end-exhalation scans. The DVFs associated with the end-exhalation to end-inhalation CTs (generated from the 5DCTs 36) were computed using an in-house optical flow registration and then used as the ground-truth displacement for the inverse elasticity estimation process 37, 38. The resulting elasticity distribution, the deformation vector field, and the source geometry were assigned the label and the data for the learning process, respectively. The training process iterated for a fixed number of generator and discriminator updates.

For our validation study, we compared the deformations obtained from the DNN generated model with the deformation vector fields of the ground-truth 4DMR datasets representing different breathing phases.

For *Medical Requirements and Assessment*, the work accomplished by the group has greatly advanced our understanding of the mechanics of liver tissue as it responds to surgical and non-surgical trauma. We are able to visualize bleeding injuries and create liver deformations with external pressure as is produced during surgery. The mathematical and hyperelastic models of the liver have been produced, a major leap in biologic modelling.

- **What was the impact on technology transfer?**

For *Numerical Methods for Real-Time Modeling*, the worked supported by this effort resulted in 5 published papers, 1 submitted papers, and 1 in preparation paper.

For *Biomechanical and Graphical Modeling of Organs,* two disclosures are being prepared:

  - 4DMR guided liver elastography
  - Liver model for CT/MR calibration and commissioning

For *Medical Requirements and Assessment*, the numerical and empiric methods created during the course of this project are being made available to the public. We hope for the passive dissemination of our findings by interested parties.

- **What was the impact on society beyond science and technology?**

For *Numerical Methods for Real-Time Modeling*, simulation of surgery will have a transformative effect on medicine and how surgeons are trained. Our efforts have helped to make these transformative techniques a reality.

For *Biomechanical and Graphical Modeling of Organs*, the impact will be further quantitatively known when the product will be commercialized.

For *Medical Requirements and Assessment,* the development of the visco-elastic model of liver deformations paired with physiologic, high-fidelity simulations of the autonomic system will impact society in numerous ways. Currently, medical simulation has limited capability in modeling tissue deformations and physiologic derangements such as hemorrhage realistically. This work will allow for improved medical training and patient management in emergency, combat scenarios as well as patient-centered care with models that will aid surgeons in surgical planning of routine major surgery.

CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

Nothing to Report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

Longtime faculty member, co-investigator, and key personnel Dr. Warren Grundfest, passed away in late December 2018 after a long illness. In January, after his passing, we began the process, which is ongoing, of reviewing the status of all of his research activities and relationships, as well as the laboratory equipment and facilities under his purview and planning appropriate transitions and dispositions for all involved. Dr. Grunfest's efforts interfaced with those of the other project investigators and will continue under a combination of direction from other faculty involved in the project, primarily Dr. Erik Dutson, with some involvement from Prof. Jeff Eldredge and Prof. Joseph Teran, in addition to guidance from our PI, Dr. Peyman Benharash and from co-investigator Anand Santhanam.

At this stage we do not anticipate bringing a new faculty investigator on board to replace Dr. Grundfest in his role on the project. Our existing relationships are sufficient to complete the project.

We have, however, experienced delays in completion of the work and have therefore requested an additional 1-year no-cost time extension, which will be sufficient to complete the project.

- **Changes that had a significant impact on expenditures**

Nothing to Report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report.

- **Significant changes in use or care of human subjects**

Nothing to Report.

- **Significant changes in use or care of vertebrate animals.**

Nothing to Report.

- **Significant changes in use of biohazards and/or select agents**

Nothing to Report.

PRODUCTS:

- **Publications, conference papers, and presentations**

S. Wang, M. Ding, T. Gast, L. Zhu, S. Gagniere, C. Jiang, J. Teran, *Simulation and Visualization of Ductile Fracture with the Material Point Method*, In Review.

Q. Guo, X. Han, C. Fu, T. Gast, R. Tamstorf, J. Teran, *A Material Point Method for Thin Shells with Frictional Contact*, ACM Transactions on Graphics (SIGGRAPH 2018), 37(4), pp. 147:1-147:15, 2018.

C. Fu, Q. Guo, T. Gast, C. Jiang, J. Teran, *A Polynomial Particle-In-Cell Method*, ACM Transactions on Graphics (SIGGRAPH Asia 2017), 36(6), pp. 222:1-222:12, 2017.

C. Jiang, T. Gast, J. Teran, *Anisotropic Elastoplasticity for Cloth, Knit and Hair Frictional Contact*, ACM Transactions on Graphics (SIGGRAPH 2017), 36(4), pp. 152:1-152:14, 2017.

A. Pradhana, T. Gast, G. Klar, C. Fu, J. Teran, C. Jiang, K. Museth, *Multi-species Simulation of Porous Sand and Water Mixtures*, ACM Transactions on Graphics (SIGGRAPH 2017), 36(4), pp. 105:1-105:12, 2017.

G. Klar, T. Gast, A. Pradhana, C. Fu, C. Schroeder, C. Jiang, J. Teran, *Drucker-Prager Elastoplasticity for Sand Animation*, ACM Transactions on Graphics (SIGGRAPH 2016), 35(4), pp. 103:1-103:12, 2016.

Hasse K, Han F, Neylon J, Min Y, Hu P, Yang Y, and Santhanam A.P. 2018. *Estimation and validation of patient-specific liver elasticity distributions derived from 4DMR*. Biomedical Physics and Engineering Express 4(4).

Hasse K, Neylon J, and Santhanam A.P. 2017. *Feasibility and quantitative analysis of a biomechanical mode-guided lung elastography for radiotherapy.* Biomedical physics and engineering express 3(2).

Santhanam A.P., Hasse K, Stiehl B, and Low D. 2018. *A Generative Adversarial Network based biomechanical model of liver for model guided liver deformable image registration*, In Preparation

Santhanam A.P., Hasse K, Stiehl B, and Low D. 2018. *Simulating surgical procedures using an AI based liver deformation model*, In Preparation

Li, L., Maccabi, A., Abiri, A., Juo, Y.Y., Zhang, W., Chang, Y.J., Saddik, G.N., Jin, L., Grundfest, W.S., Dutson, E.P. and Eldredge, J.D., 2019. *Characterization of perfused and sectioned liver tissue in a full indentation cycle using a visco-hyperelastic model.* Journal of the mechanical behavior of biomedical materials, *90*, pp.591-603.

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Professor Jeff D. Eldredge, Ph.D. (no change)
Name:	Dr. Kwitae Chong, Ph.D. (no change)
Name:	Mr. Daniel Canuto (no change)
Name:	Mr. Yi-Jui Chang (no change)
Name:	Joseph Teran, Ph.D. (no change)
Name:	Chenfanfu Jiang, Ph.D. (no change)
Name:	Qi Guo (no change)
Name:	Dr. Chuyuan Fu, Ph.D. (no change)
Name:	Theodore Gast, Ph.D. (no change)
Name:	Xuchen Han (no change)
Name:	Mengyuan Ding (no change)
Name:	Stephanie Wang (no change)
Name:	Anand Santhanam (no change)
Name:	Michael Reyes (no change)
Name:	Robert Candler (no change)
Name:	Dr. Warren Grundfest (passed away December 2018)
Name:	Ms. Ling Li (no change)
Name:	Mr. Ashkan Maccabi (no change)
Name:	Mr. Ahmad Abiri (no change)
Name:	Dr. George Saddik (no change)
Name:	Dr. Nathan Francis (no change)
Name:	Demetri Terzopoulos (no change)
Name:	Tao Zhou (no change)
Name:	Peyman Benharash (no change)
Name:	Erik Dutson (no change)
Name:	Yen-Yi Juo (no change)
Name:	Yas Sanaiha (no change)
Name:	Cheryl Hein (no change)

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report.

- **What other organizations were involved as partners?**

Nothing to Report.