Understanding the Mechanical and Morphological Properties of the Pediatric Skull

A Thesis

Presented to

the faculty of the School of Engineering and Applied Science

University of Virginia

In partial fulfillment

of the requirements for the degree

Master of Science by

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May 2020

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is submitted in partial fulfillment of the requirements for the degree of

Master of Science

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ABSTRACT

Pathological conditions of the pediatric craniofacial skeleton commonly occur from traumatic injuries and congenital birth defects. Corrective surgeries are often necessary to treat these conditions. Due to the capacity for rapid growth of the developing pediatric skull, these surgeries involve removing large portions of the pathological skull tissue, and relying on the regrowth of the skull tissue. There are a number of challenges associated with these corrective surgeries stemming primarily from a lack of information and understanding of the properties and growth of the pediatric skull. These challenges include an elevated risk of skull fracture from surgical defects, an incompatibility of surgical hardware originally designed for adult skull tissue and scaled in size for children, and an unknown regrowth pattern of the skull following the surgery. Improving our understanding of the pediatric skull, both in terms of mechanical property information and the development patterns of the pediatric skull with age, will ultimately help reduce the challenges with pediatric craniofacial surgery. Therefore, the goal of this research is to improve our understanding of the pediatric skull by using a two-phased approach. The first phase involved experimental testing of pediatric cranial bone to identify its microstructure and mechanical properties. The second phase involved developing an analytical model of pediatric skull tissue growth, applying this model to a computational framework that simulates the growth and development of a skull from 6 months to 2 years in age, and then investigating how parameters in the tissue growth model influence the prediction of the pediatric skull shape, mechanical properties, and skull thickness.

In the first phase, eight fresh, never frozen, pediatric skull tissue specimens were collected in the operating room during pediatric craniosynostosis surgery. The normally discarded tissue was obtained from patients ranging in age from 4 to 10 months. Up to 12 individual samples were harvested and prepared from each specimen for mechanical four-point bending testing to failure. The microstructure of each sample was analyzed using micro-computed tomography before and after each mechanical test. From this analysis, effective geometric and mechanical properties were determined for each sample (n = 68). Test results demonstrated that the pediatric skull is 2.0 mm (+/- 0.4) thick, with a porosity of approximately 80%, The effective Young's modulus of the pediatric skull tissue, determined using Euler beam theory, was 4.2 GPa (+/- 2.1), which was approximately three times less stiff than adult skull tissue reported in the literature. Furthermore, the pediatric skull was able to bend up to tensile failure strains of 6.7% (+/- 2.0), which was approximately five times larger than failure strains measured in adult skull. The disparity between the measured mechanical properties of pediatric skull tissue and adult skull tissue highlights the need to reevaluate the design of surgical hardware used in pediatric cranial surgery to be more compatible with the pediatric tissue.

Using the mechanical data collected in this study, the second phase of the research involved the development of a computational model of skull growth to investigate how the natural growth and expansion of the pediatric brain influence the shape and structural growth patterns of the pediatric skull. Skull tissue growth was modeled by simulating bone remodeling (resorption and growth) using the biomechanical loading (tissue stresses and strains) distributed throughout the pediatric skull during brain growth. This tissue growth model was implemented into a finite element (FE) model of a 6-month old pediatric skull that was developed using published skull morphology data. An iterative growth process was applied to the FE model, with each iteration corresponding to discrete week in age. For each iteration, the biomechanical responses of the skull model were calculated through simulation of an increment of brain volume corresponding to natural growth rates. The resulting loading distribution calculated throughout the skull model was used to update the skull tissue geometry, modulus, and thickness based on a skull tissue growth model. Simulations of growth were performed up to 2 years of age, and the final skull shape and stiffness was validated against limited available literature. Furthermore, a parametric analysis was performed to investigate the factors contributing to the underlying growth patterns of the skull. This pediatric skull growth model was the first of its kind in the field, and with the wider availability of pediatric data, it serves as a platform for future development and capability as a tool to predict healthy and post-operative pediatric skull growth.

Overall, the insight from this thesis will help to address the underlying challenges associated with pediatric craniofacial surgeries. By facilitating development of surgical hardware that is specific to the unique characteristics of the pediatric skull and enabling understanding of the growth patterns of the pediatric skull, the work of this thesis will comprehensively maximize the well-being of pediatric surgical patients moving forward.

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CHAPTER 1: INTRODUCTION

1.1. Motivation

Pathological conditions of the pediatric craniofacial skeleton are commonly attributed to traumatic injuries and congenital birth defects. Within the pediatric population, head injury is the most common cause of death and disability, resulting in over 2,500 deaths, 37,000 hospitalizations, and 435,000 emergency department visits annually (Frieden et al. 2010). In addition, congenital birth defects impacting the development of the skull occur in around 1 in every 2500 births (Johnson & Wilkie 2011).

Compared to all other age groups, the pediatric population is most susceptible to developing craniofacial pathologies. There are several reasons why this may be the case, including greater cranial mass-to-body and volume-to-body ratios for the pediatric population; however, the most probable contributing factor stems from the structural and material characteristics of the pediatric skull (Haug & Foss 2000; Arbogast & Maltese 2015).

The skull grows rapidly during the initial stages of life, attaining approximately 75% of its final adult size by the end of the second year of age (Huelke 1998). To expand in such a rapid fashion, certain structural characteristics are necessary. The pediatric skull consists of several individual bones joined by fibrous connective tissues, known as sutures, which enable compliancy of the bones relative to one another (Idriz et al. 2015). Sutures begin to close once the period of rapid skull growth has concluded, joining the bones into a contiguous structure. In some cases; however, pathological conditions can disrupt normal closure of the sutures. One such condition known as craniosynostosis causes these sutures to close prematurely, preventing proper expansion of the skull and consequently impacting both structural and cognitive development (Johnson & Wilkie 2011).

Microstructurally, skull bones initially form as a single, solid cortical layer which later differentiates into a tri-layer configuration that consists of inner and outer solid cortical tables surrounding a porous diploe layer (Crandall et al. 2013). This single- to tri-layer transformation occurs during the first few months of life, with the bone retaining a tri-layer structure into adulthood. Although the tri-layer configuration is present within both adult and pediatric populations, it is known that pediatric skull bone behaves differently than adult skull bone under loading, specifically exhibiting greater flexibility and less stiffness, and that these loading differences can be attributed to variations in composition, rigidity, and structure (Crandall et al. 2013; Winkelstein 2013). The heightened susceptibility to craniofacial trauma within the pediatric population can likely be attributed to these structural and corresponding behavioral differences under loading.

1.1.1. Experimental Data for the Pediatric Skull

There is currently a paucity of data concerning the mechanical properties of the pediatric skull (Arbogast & Maltese 2015). The entire body of knowledge consists of small case studies on fresh-frozen cranial tissue from pre-term infants (McPherson & Kriewall 1980; Kriewall 1982), infants (Margulies 2000; Coats & Margulies 2006), and a single-specimen study on a 6-year-old (Davis et al. 2012). Due to this lack of existing knowledge and despite the understood differences between pediatric and adult skull bone, surgical treatments for both pediatric cranial injuries and pathological conditions are currently based on methodologies and materials that were developed for the adult population, potentially resulting in suboptimal impacts on pediatric patient outcomes. Greater availability of data regarding the mechanical properties and microstructural characteristics of the pediatric skull would enable the development of surgical tools and fixation hardware that is

better suited for the pediatric population, correspondingly improving the long-term well-being of pediatric surgical patients.

1.1.2. Computational Growth Modeling of the Pediatric Skull

Finite element (FE) modeling is a computational tool that has been successfully used to analyze the response of biological models to a wide variety of loading conditions. While a number of pediatric cranial FE models have been developed to better understand pediatric head injuries in response to externally applied forces, there has been limited insight into the growth patterns of the pediatric skull in response to the underlying internal mechanical forces imparted during the growth process, specifically from the expanding brain (Libby et al. 2017). It is known that the pediatric skull grows rapidly during the initial stages of life; however, it is currently unknown what specific factors contribute to this observed growth and how those factors inform the underlying morphology of the developing skull (Lee et al. 2019). A better understanding of the factors contributing to growth of the pediatric skull through computational modeling of the growth process would allow for development of surgical methodologies and planning practices that are tailored towards enabling optimal patient outcomes over time.

1.2. Objectives

The overall goal of this thesis was to improve our understanding of the pediatric skull. In accomplishing this goal, two fundamental questions were addressed. First, what are the mechanical properties of the pediatric skull under loading? Second, how can we predict pediatric skull growth patterns with aging? Addressing these questions will provide a better comprehensive understanding of the pediatric skull, both in terms of mechanical and morphological properties, which will facilitate improvements in pediatric surgical materials and methodologies as well as enhanced pediatric FE models. The goal of this thesis and these fundamental questions will be addressed through two phases.

- 1. Determination of the microstructural and mechanical properties of pediatric skull tissue.
- 2. Development of a pediatric skull tissue growth model and implementation of the model into a computational framework to predict pediatric skull growth.

Pediatric cranial bone will be analyzed by performing mechanical tests and microcomputed tomography (micro-CT) on pediatric cranial bone specimens to determine material and structural characteristics. A pediatric skull growth FE model will be developed and evaluated using LS-DYNA (Livermore Software Technology Corporation, Livermore, CA) and MATLAB (Mathworks, Natick, MA) to simulate growth of a baseline pediatric cranial FE model through an iterative process over time in response to different model inputs.

1.3. Expected Contributions

In accomplishing the tasks of this thesis, there are several expected contributions to the fields of experimental and computational biomechanics.

First, there is very limited data concerning the microstructural and mechanical properties of the pediatric skull. Mechanical property data does exist; however, the bulk of the data was obtained using samples collected from pre-term infants, which contain a single-layer bone structure differing from that of the tri-layer structure seen in older infants. Due to the lack of experimental data and the inherent biological variability of that data, this study performed additional mechanical tests on pediatric cranial bone to expand upon the existing body of mechanical property data. Additionally, to perform these mechanical tests, a custom-designed test rig was to conduct additional mechanical tests on biological materials. Second, while the general microstructural characteristics of pediatric cranial bone have been documented, the microstructural characteristics have not been specifically quantified. Additionally, structural data has not been used to calculate mechanical properties, even though this knowledge would enhance the accuracy and corresponding value and applicability of those properties within a wide range of settings. This research quantified the structural characteristics of the pediatric skull and provided mechanical properties using those structural characteristics to more accurately determine the value of the properties.

Third, there has been limited computational investigation into the developmental patterns of the pediatric skull, with prior computational studies focusing primarily on the tolerance of the skull to external loads. This study was the first to investigate the developmental patterns of the pediatric skull by creating a computational growth model. Using this model, a range of input parameters were investigated to determine their impact on skull growth pattern. Due to a lack of existing pediatric data, the growth model was not fully validated, but it was intended to act as a framework for future development in this research area. With greater availability of knowledge regarding the pediatric skull developmental processes, both in terms of regular developmental patterns and the underlying factors contributing to those developmental patterns, a more comprehensive understanding pediatric cranial growth can be obtained. The future versions of this model are expected to aid in surgical planning procedures, where surgeons could implement simulated surgical treatments for pediatric cranial pathologies and the model could be leveraged to predict the long-term response to that pathology, ensuring the optimal surgical treatment is applied to maximize the future well-being of a pediatric surgical patient.

CHAPTER 2: BACKGROUND

This chapter provides an overview of the anatomy and developmental process of the skull, specifically highlighting differences between those of the adult and pediatric populations. Additionally, background information pertaining to prior pediatric skull experimental and computational studies will be provided, and used, where appropriate, to guide the areas of emphasis of this thesis.

2.1. General Cranial Anatomy

The human skull is a bony structure that primarily functions to protect the brain and to support the various structures and soft tissues of the head (Scheuer & Black 2004). It consists of two sections known as the neurocranium and the viscerocranium (Figure 2-1) (Scheuer & Black 2004). The neurocranium, also referred to as the braincase, calvarium, or cranial vault, forms the superior and posterior portions of the skull (Winkelstein 2013). It acts as a protective region surrounding the brain and is comprised of seven primary bone plates, including the left and right frontal bones located in its anterior region, the left and right parietal bones located along its superior region, the left and right temporal bones and the sphenoid bone located along its base and lateral walls, and the occipital bone in its posterior region (Figure 2-1) (Scheuer & Black 2004). The viscerocranium forms the anterior portion of the skull and consists of the structures that comprise the face and the mandible (Figure 2-1) (Scheuer & Black 2004).



Figure 2-1: Sagittal plane view of the adult skull divided into the neurocranium (shown with colored structures) and the viscerocranium (shown in white) (Adapted from Lumen Learning).

2.2. Pediatric Cranial Anatomy and Development

The skull undergoes rapid development between birth and two years of age, with the brain reaching nearly 75% of its adult volume and 80% of its adult mass during this time (Huelke 1998; Casey et al. 2000). To enable this magnitude of growth, the pediatric skull must be flexible. It contains two types of fibrous regions, known as sutures and fontanelles, that connect the bony plates of the neurocranium to allow the brain to grow.

Sutures occur at the interface of two bone plates and fontanelles, or soft spots, occur at the interface of three or more bone plates (Arbogast & Maltese 2015). Sutures and fontanelles allow the plates of the neurocranium to move relative to one another, which is critical during the birth process (Opperman 2000). In addition, they act as fronts for bone growth to accommodate the rapid expansion of the brain during early phases of development (Opperman 2000). They do this by enabling the bone plates to change in morphology by expanding perpendicular to the cranial bone edges over the growing brain (Katsianou et al. 2016). As the skull grows, the sutures and fontanelles close. Fontanelles regularly close during early childhood, and as the skull approaches

its final volume later in childhood, the sutures begin to narrow and close. At this point in the developmental process, the plates of the neurocranium fuse to one another (Figure 2-2) (Arbogast & Maltese 2015). This results in an essentially contiguous and rigid structure that encases the brain, which is fully evident by adulthood.



Figure 2-2: Superior aspects of the adult (left) and pediatric (right) skulls showing various anatomical features and structural differences, with adult skulls exhibiting fused fontanelles and sutures (Adapted from Arbogast & Maltese 2015).

2.2.1. Suture and Fontanelle Anatomy

There are several primary sutures joining the bone plates of the pediatric neurocranium. These include the metopic, sagittal, coronal, squamosal, and lambdoid sutures. The metopic suture separates the left and right frontal bones, running along the sagittal plane of the skull. Also running along the sagittal plane, the sagittal suture separates the left and right parietal bones. The coronal sutures, existing on the lateral faces of the neurocranium, separate the left frontal and parietal and the right frontal and parietal bones from one another. On the lateral faces of the neurocranium, the squamosal sutures separate the parietal and temporal bones from one another on both the left and right faces of the neurocranium. Finally, at the posterior portion of the neurocranium, the lambdoid sutures separate the occipital bone from the left and right parietal bones. Each of these sutures narrow gradually with aging before complete closure and bone fusion occurs (Crandall et al. 2013). Typically, the metopic suture is the first to close, occurring during early adolescence (Idriz et al. 2015). Aside from the metopic suture, the other sutures of the neurocranium remain patent through adolescence and into adulthood, albeit with a very limited degree of compliance (Idriz et al. 2015). The locations of each of the cranial sutures are shown in Figure 2-3.

There are four primary fontanelles which separate the sutures of the skull. Along the sagittal plane of the skull, the anterior fontanelle occurs at the interface of the metopic, sagittal, and coronal sutures. Also along the sagittal plane, the posterior fontanelle occurs at the interface of the sagittal and lambdoid sutures. Present on the left and right lateral faces of the skull, the sphenoidal fontanelles exist at the interface of the squamosal and coronal sutures and the mastoid fontanelles exist at the interface of the squamosal and lambdoid sutures. In general, the fontanelles remain patent through the first few months to first two years of life (Crandall et al. 2013). Each fontanelle is shown in Figure 2-3 below.



Figure 2-3: Pediatric skull suture and fontanelle anatomy with primary ossification centers seen as highlighted white areas on the skull bone surfaces (Adapted from Crandall et al. 2013).

2.2.2. Pediatric Cranial Growth

As previously mentioned, sutures act as growth sites for the bony plates of the neurocranium. During expansion of the skull, sutures act as bone growth sites by enabling these bony plates to move away from one another (Opperman 2000). This separation of the bony plates of the neurocranium provides a location for expansion of the osteogenic bone fronts, enabling bone growth (Opperman 2000).

At a cellular level, bone growth occurs at these osteogenic bone fronts, seen as the white locations on the skull surface in Figure 2-3, in response to biomechanical signals induced by the expanding brain (Katsianou et al. 2016). While it is currently unclear which signaling factors induce bone growth at the sutures, it has been shown that these factors likely result from mechanical strain occurring across the suture (Opperman 2000; Katsianou et al. 2016). The presence of strain disturbs the collagen fibers within the suture which causes them to undertake different orientations and correspondingly trigger cells at the sutures to undergo osteoblast differentiation and subsequent bone ossification (Katsianou et al. 2016). The continued mechanical strain induced by the expanding brain allows the sutures to remain patent, providing a front for continued osteoblast differentiation and bone ossification (Katsianou et al. 2016). In the absence of sufficient mechanical strain with the slowing of brain growth, these mechanical stimuli are no longer present, causing the front for new bone growth to close. The closure of the bone growth front results in the ossification of the sutures, which occurs progressively between adolescence and adulthood (Katsianou et al. 2016).

2.3. A Pathological Condition Impacting Cranial Growth

Since pediatric skull growth occurs at the interface of bone and suture, any disruption of this interface has the potential to cause growth and development abnormalities. Craniosynostosis is one such disruption to normal cranial growth. This pathological condition is characterized by

the premature fusion of cranial sutures, occurring when the two bones on either side of the suture join prematurely and develop an increased thickness, eliminating the suture and consequently eliminating the front for cranial growth in that region of the skull (Goos & Mathijssen 2019; Johnson & Wilkie 2011). The prevalence of craniosynostosis within the pediatric population has been estimated at between 1 in 2100 and 1 in 2500 births (Lajeunie et al. 1995; Boulet et al. 2008). It is thought to occur as a result of a genetic alteration or mutation (Goos & Mathijssen 2019). Since the brain continues to expand with aging, the consequence of cranial suture fusion is that that head cannot grow in that region and simultaneously experiences overcompensated growth in another region where the sutures have not yet fused (Johnson & Wilkie 2011). Not only does this result in an abnormal cranial shape, but it also imparts an irregular distribution of pressure on the growing brain which has the potential to cause complications associated with sensory, respiratory, and neurological functionality (Johnson & Wilkie 2011).

There are several types of craniosynostosis that are characterized by the specifically affected suture. The sutures commonly impacted by craniosynostosis include the sagittal, coronal, lambdoid, and metopic sutures, with sagittal craniosynostosis being the most common and lambdoid craniosynostosis being the least common (Mayo Clinic). Premature fusion of each of these sutures results in a different cranial shape abnormality, and multiple sutures can be fused in a single case. Sagittal synostosis forces the head to grow long and narrow (scaphocephaly), metopic synostosis causes the head to develop a triangular appearance (trigonocephaly), coronal synostosis causes the forehead to flatten and the head to become short and wide in appearance (brachycephaly), and lambdoid synostosis causes the head to develop a flattened shape (plagiocephaly) (Figure 2-4) (Mayo Clinic; Goos & Mathijssen 2019). Craniosynostosis is commonly diagnosed by clinical specialists through physical examination. Premature fusion of

sutures will result in ridges at the suture sites, the noticeable lack of fontanelles on the head, and visible facial deformities (CDC). Additionally, CT and MRI imaging are used to identify the specific configuration of the fused suture (CDC).



Figure 2-4: Different variations of craniosynostosis result in different associated cranial shape abnormalities during the growth process (Adapted from Goos & Mathijssen 2019).

There are several treatment options for craniosynostosis, including wearing a special helmet to guide the shaping of the skull with brain growth, endoscopic surgery, and open surgery (Mayo Clinic). The endoscopic surgery option is minimally invasive and involves making small scalp incisions and excising the affected suture to enable normal skull expansion (Mayo Clinic). This surgical approach is intended for young infants (less than 6 months of age) and is typically reserved for less severe cases (Mayo Clinic). Open surgery, on the other hand, is performed for more severe cases on infants typically up to 1-year old (Mayo Clinic). This procedure involves making an incision in the scalp and removing sections of cranial bone to reshape the configuration of the skull. In some cases, the skull position is held in place with plates and screws which are resorbed over time, and in others, the specific patterning of the bone removal guides skull growth to develop a normal configuration on its own through the imparted pressure distribution (Mayo Clinic). After treatment, infants affected by craniosynostosis will develop more normal skull shapes within a matter of months, allowing them to experience proper physical and cognitive growth and development moving forward.

2.4. Pediatric and Adult Skull Differences

The newborn skull is approximately 25% of the size of the adult skull in terms of both volume and mass (Prange et al. 2004; Prasad et al. 1985). However, despite the similar scale factor for both of these parameters, the pediatric skull cannot simply be considered a miniaturized version of the adult skull (Loyd 2011). In addition to possessing sutures to accommodate rapid growth and expansion, as noted previously, the pediatric skull also contains geometric and microstructural differences which further differentiate it from the adult skull (Loyd 2011).

2.4.1. Geometric Differences

The head of an infant comprises nearly 25% of the total body height, while the head of an adult makes up only 14% of total body height on average (Figure 2-5a) (Huelke 1998). When considering skull volume, the brain comprises a greater proportion of the total skull volume in the infant as compared to the adult, meaning the viscerocranium, which encompasses the brain, is proportionally larger in infants as well (Loyd 2011). Since the viscerocranium is proportionally larger in infants than adults, this means that the facial region of infants is proportionally smaller than that of adults (Huelke 1998). Due to these differences in surface area coverage of the viscerocranium and facial regions, the pediatric skull exhibits a more spherical and rounded morphology as opposed to the adult, which has a more oval-shaped configuration when viewed in the sagittal plane, as seen in Figure 2-5b (Silau et al. 1995). Additionally, as mentioned previously, the presence of sutures and fontanelles within the pediatric skull enables greater flexibility of the complete skull structure as compared to the rigid adult skull, resulting in different behaviors in response to external forces.



Figure 2-5: The head height of an infant is proportionally greater than that of an adult (a), and infant heads are more rounded with smaller facial regions than those of adults (b) (Adapted from Huelke 1998).

2.4.2. Microstructural Differences

From a microstructural standpoint, the bony structure of the pediatric skull differs from the adult skull in terms of composition, rigidity, and structure. Adult cranial bone exhibits thicknesses exceeding 5mm throughout the skull, whereas pediatric cranial bone is considerably thinner at around 1mm on average at birth (Motherway et al. 2009; Crandall et al. 2013). At birth, pediatric skull bone typically consists of a single, solid layer of cortical bone (Crandall et al. 2013). With the progression of aging, the single cortical layer will differentiate into a tri-layer structure consisting of an inner and outer cortical table surrounding a center diploe layer (Figure 2-6) (Crandall et al. 2013). This tri-layer structure develops within the first few months of life and persists into adulthood. Though this tri-layer structure is also present within the adult population, it is known that pediatric skull bone behaves differently than adult skull bone under loading, possessing considerably lower stiffness and considerably greater flexibility.



Figure 2-6: Pediatric skull bone structure progresses from a single cortical layer to a tri-layer configuration with inner and outer cortical tables and a center diploe layer which persists into adulthood.

Another documented difference between adult and pediatric cranial bone is that pediatric cranial bone possesses a noticeable directional fiber orientation as opposed to adult cranial bone which possesses an essentially uniform configuration (Crandall et al. 2013). The reason for this directionality is that the pediatric skull contains ossification centers at several locations throughout the skull, represented as the bright-colored regions on each cranial bone plate in Figure 1-6 above (Crandall et al. 2013). Bone growth occurs radially outward from each of these ossification centers due to the secretion of bone morphogenic proteins (BMPs) (Lee et al. 2019). These BMPs signal osteoblast differentiation and subsequent bone formation which occurs along fibers (Lee et al. 2019). Bone formation along fibers within the cranial bone plates causes pediatric cranial bone to exhibit a directionality in stiffness, with greater stiffness in orientations parallel to fibers and less stiffness in orientations perpendicular to fibers (Arbogast & Maltese 2015). With the conclusion of growth, however, these ossification centers are no longer present, meaning there is no longer a directionality for bone growth (Crandall et al. 2013). As a result, there is not a demonstrated difference in stiffness with respect to loading orientation within the adult skull (Crandall et al. 2013).

The compositional and structural differences between pediatric and adult skull bone can likely be attributed in part to the loading conditions each are subjected to over time (Weinans et al. 1992). It has been shown that general bone growth and remodeling is instigated by localized mechanical stimuli, specifically stresses and strains, which activate bone growth regulation cells such as osteoblasts and osteoclasts within the bone matrix (Weinans et al. 1992). Activation of these specialized cells initiates local bone growth or resorption depending on the stimulus magnitude causing variations in localized bone structure.

In general, variations in localized bone structure result in different behaviors under loading and corresponding differences in bone stiffness and flexibility (Weinans et al. 1992). For the skull, differences in localized mechanical stresses and strains applied to the bone tissue of pediatric individuals and adults result in compositional and structural variations due to the differences in activation of bone growth regulatory cells. These compositional and structural differences likely play a role in the observed differences in stiffness and flexibility observed between pediatric and adult cranial bone.

2.5. Previous Pediatric Skull Research

Previous studies investigating the pediatric skull have focused on both mechanical testing and computational modeling. In its current state, the limited quantity of pediatric skull research highlights the need for better understanding of the pediatric skull moving forward. The contributions of prior experimental and computational pediatric skull studies are outlined below.

2.5.1. Prior Experimental Studies

While a multitude of mechanical tests of adult cranial bone under compression, tension, bending, and shear have been performed in literature, there is a paucity of available information for the developing pediatric population (Arbogast & Maltese 2015). Not only are pediatric donors

not widely available, but sensitivity associated with testing material obtained from pediatric donors further limits experimental efforts. The entire body of knowledge regarding pediatric cranial material properties consists of small case studies on fresh-frozen cranial tissue from pre-term infants (McPherson et al. 1980; Kriewall et al. 1982), infants (Margulies et al. 2000; Coats et al. 2006; Wang et al. 2014), and two single-specimen studies on 6-year-olds (McPherson et al. 1980; Davis et al. 2011). Each of these tests was subjected to limited availability of samples, and, as is typical with the nature of all human tissue tests, a high degree of biological variability both for samples from the same test specimen and for samples across multiple test specimens. Each of these studies will be briefly outlined in terms of the test specimens, the test methods employed, and the general findings. Table 2-1 summarizes the methods and sample sizes for prior studies. Complete mechanical property results for each study are shown in Appendix A.

McPherson et al. (1980) obtained parietal cranial bone specimens from six pre-term infants and one 6-year-old child. For the pre-term infant specimens, samples were prepared both parallel and perpendicular to the observed ossification center fibers, and for the 6-year-old child specimen, samples were prepared parallel and perpendicular to the sagittal suture. For each sample, threepoint bending tests were conducted to failure after sample preconditioning. From the study, it was found that elastic modulus for samples oriented parallel to the fiber direction increases as subject age increases, modulus is greater for specimens tested parallel to fiber direction as opposed to perpendicular, and the difference in modulus with the direction of loading was still evident in the 6-year-old child specimen but was not evident in adults.

Table 2-1: Summary of prior experimental studies of pediatric cranial bone displaying the testing methods employed and sample information. Complete mechanical property results for each study are shown in Appendix A.

Author (Year)	Testing Method	Bone Tested	Specimen Age Range (Months Post-Gest.)	Suture Orientation to Sample	Total Specimens	Total Samples
McPherson & Kriewall (1980)	3-Point Bending	Parietal	-3.4 to 0	Parallel	6	27
				Perpendicular	8	47
		Frontal	0	Parallel	2	7
				Perpendicular	2	7
		Parietal	72	Parallel	1	6
				Perpendicular	1	6
Kriewall	Whole-		-4.5 to 0.5	Parallel	16	16
(1982)	Bone Flexion	Parietal		Perpendicular	16	16
Margulies	3 Doint		-3.4 to 0	Parallel	3	8
& Thibault (2000)	Bending	Parietal	6	Parallel	1	4
	3-Point Bending	Parietal	-2.7 to -0.2	Parallel	4	6
			0.6 to 4.5	Parallel	7	10
Coats &			11 to 13	Parallel	3	5
(2006)		Occipital	-4.4 to -0.2	Parallel	6	9
(2000)			0.7 to 4.5	Parallel	7	12
			11 to 12	Parallel	2	4
Davis et al. (2011)	4-Point Bending	Parietal (Cortical)	72	Perpendicular	1	7
		Parietal (Tri- Layer)	72	Perpendicular	1	11
		Frontal (Tri- Layer)	72	Perpendicular	1	6
Wang et	3-Point	Parietal	12 to 24	Perpendicular	7	14
al. (2014)	Bending	Frontal	12 to 24	Perpendicular	7	14

McPherson et al. (1980) obtained parietal cranial bone specimens from six pre-term infants and one 6-year-old child. For the pre-term infant specimens, samples were prepared both parallel and perpendicular to the observed ossification center fibers, and for the 6-year-old child specimen, samples were prepared parallel and perpendicular to the sagittal suture. For each sample, threepoint bending tests were conducted to failure after sample preconditioning. From the study, it was found that elastic modulus for samples oriented parallel to the fiber direction increases as subject age increases, modulus is greater for specimens tested parallel to fiber direction as opposed to perpendicular, and the difference in modulus with the direction of loading was still evident in the 6-year-old child specimen but was not evident in adults.

Kriewall et al. (1982) tested 20 whole parietal cranial bone samples obtained from 10 fetal calvaria to measure whole-bone stiffness. This was done by performing a preconditioning procedure before applying a force to the inner face of the parietal bone resulting in a deflection of the bone specimen (Figure 2-7). This deflection was then related to the magnitude of the force to quantify stiffness. From the study, it was found that stiffness was greater parallel to bone fiber orientation as opposed to perpendicular to fiber orientation.



Figure 2-7: Schematic of whole parietal bone testing setup used by Kriewall et al. (1982).

Margulies et al. (2000) tested bilateral strips of parietal cranial bone obtained from 4 pediatric subjects ranging from pre-term to 6-months of age. Samples were prepared parallel to the sagittal suture and were then tested to failure under three-point bending at both quasi-static and

dynamic loading rates. From the study, it was found that modulus increased with loading rate and that both modulus and ultimate stress increased with age.

Coats et al. (2006) obtained 23 calvaria from pediatric subjects ranging in age from preterm to 1-year old. Samples were prepared and tested perpendicular to the orientation of ossification fibers for parietal and occipital bones under three-point bending at dynamic loading rates (Figure 2-8a). Additionally, tensile tests were conducted on coronal suture specimens (Figure 2-8b). From the study, it was found that modulus and ultimate stress both increase with age, cranial bone was significantly stiffer than suture, parietal bone modulus and ultimate stress were significantly greater than that of occipital bone, age did not significantly influence suture modulus, and strain rate did not have a significant effect on modulus and ultimate stress but did impact ultimate strain, within the pediatric population tested.



Figure 2-8: Schematic of sample characteristics and experimental tests performed by Coats et al. (2006) on parietal and occipital pediatric cranial bone specimens under three-point bending (a) and on coronal suture specimens under tension (b).

Wang et al. (2014) measured the mechanical properties of cranial bone and suture specimens obtained from seven pediatric subjects with ages between 1 and 2 years old. Bone samples were prepared from parietal bone perpendicular to the sagittal suture and from frontal

bone perpendicular to the coronal suture. Additionally, suture specimens were prepared across the sagittal and coronal sutures. All samples were tested under three-point bending conditions. From the study, it was found that within the population of test subjects, ultimate stress and modulus were greater for frontal bone than parietal bone, not significantly different for sagittal suture and coronal suture, and significantly greater for bone than suture. Additionally, it was found that ultimate strains were significantly greater for suture than for bone.

Davis et al. (2011) conducted four-point bending tests on samples prepared from a single calvarium obtained from a 6-year old subject (Figure 2-9). Samples were prepared with cross-sectional structures possessing cortical, tri-layer, and intermediate identities. The authors found that strain rate had no effect on modulus, ultimate strain, or ultimate stress across all tested samples. Additionally, they found that modulus and ultimate stress were greater for cortical bone than for tri-layer bone.



Figure 2-9: Four-point bending test setup employed by Davis et al. with noted sample measurements and bending information.

2.5.2. Previous Computational Models

Pediatric skull computational models attempt to capture both the geometric and material characteristics of the pediatric skull. Several prior computational modeling efforts for the pediatric
skull have focused on establishing normative models that represent average geometries of the pediatric population. Using a 3-year old single-subject cranial CT scan and Kriging scaling methods along with experimental validation, the PIPER child model was developed for the pediatric skull to be a continuously scalable predictor of pediatric skull geometry and material properties for the 1.5 to 6-year age range (Figure 2-10a) (Giordano & Kleiven 2016). Leveraging the CT scans of several individuals of the same age, computational models have also been developed by averaging the point clouds of the cranial surfaces determined from single-subject CT scans (Marcus et al. 2009; Yuan et al. 2016). Additionally, by averaging landmark coordinates across a database of pediatric CT scans, a continuously-scalable statistical model was developed to predict approximate skull morphologies using a common set of landmark points based on various factors including age and head circumference (Figure 2-10b) (Li et al. 2015).



Figure 2-10: Previous pediatric skull computational models include the age-scalable PIPER child model (a) developed by Giordano & Kleiven (2006) and a statistical model that predicts landmark point locations (b) developed by Li et al (2015).

A number of studies have leveraged these previously developed geometric, statistical, and finite element models or have developed finite element models from single-subject CT scans to better understand the response of the skull to loading conditions, specifically under impact. These studies have investigated the effect of various parameters on the simulated loading response of the skull through sensitivity studies by comparing to experimental datasets. Investigated parameters have included cranial suture material properties (Klinich et al. 2002; Ashok & Hu 2018) and brain material properties (Coats et al. 2007). Studies have also investigated the influence of parameters on the predicted injury tolerance and accuracy by comparing to experimental studies (Roth et al. 2009; Roth et al. 2010).

2.5.3. Previous Cranial Growth Models

Growth models predict changes in geometry and structural composition in response to mechanical stimuli such as stresses and strains. Prior growth modeling studies have primarily focused on developing algorithms to capture physiological bone remodeling in response to these stimuli (Mullender & Huiskes 1995; Weinans et al. 1992; Ruimerman et al. 2005; Coelho et al. 2009; Gerhard et al. 2009). There has been very limited investigation into pediatric skull development in response to the mechanical stimuli associated with the cranial growth process. Part of the reasoning for this limited investigation likely stems from the lack of widely available information regarding pediatric skull growth, both in terms of the typical morphology and expansion of the skull and the structural-level changes that occur with aging. Prior cranial growth modeling attempts are described below.

Libby et al. (2017) developed a baseline pediatric skull finite element model consisting of bones and sutures which was developed from a collection of CT scans. To grow the model, the intracranial volume, the region inside the skull, was expanded and the resulting general shape of the model was compared to averaged CT scans (Figure 2-11). No attempt was made to predict variations in the mechanical properties of the bone or suture tissue or to vary the thickness of the cranial bone during the growth process, both of which are known to occur with aging. In addition, due to a lack of understanding of the expansion pattern of the intracranial volume, a uniform volumetric expansion was applied. Despite the limitations, however, the model provided a good general resemblance to average clinical CT scans, indicating a positive initial approach towards pediatric cranial growth modeling.



Figure 2-11: Test methodology employed by Libby et al. which involved comparing a cranial FE model to pediatric CT scans.

Lee et al. (2019) modeled the growth pattern of a mouse cranial model by predicting cranial vault formation patterns in response to mechanical forces. To do this, the model attempted to capture the process of bone tissue ossification in response to the imposition of biomechanical stimuli to model growth of cranial bones and sutures at a molecular level (Figure 2-12). Cranial growth was prescribed by expanding the intracranial volume of the model following the known morphological developmental pattern of the mouse skull and subsequently simulating the movement of bone growth activator and inhibitor molecules under various input conditions. From this, the corresponding effect of these molecules on osteoblast production and bone growth within the model was simulated. The resulting model was iterated through multiple age steps until a final age was reached. Comparisons between the model and mouse cranial CT data indicated that the model was a good predictor of bone growth patterns. This good predictability was likely facilitated in part because the cranial mouse model was well-characterized from previous work. Due to the

lack of understanding of intracranial growth patterns as well as the absence of widely available molecular-level data for the pediatric skull, this type of detailed analysis is infeasible for humans. Despite this, the model developed by Lee et al. affords a useful framework that would be highly beneficial at predicting pediatric skull growth patterns with the wider availability of cranial growth geometric data and molecular property information.



Figure 2-12: Simulation results from Lee et al. showing the accumulated volumetric strain distribution under the prescribed growth pattern of the mouse cranial FE model used in the study. The strain distribution was used to inform bone growth within the skull.

2.6. Background Summary and Conclusions

The inherent morphological, compositional, and structural differences between the pediatric and adult skull, in combination with the paucity of available data related to pediatric skull mechanical properties and developmental patterns, points towards the need for a better comprehensive understanding of the pediatric skull. To improve this understanding, this thesis explores both the mechanical properties of the pediatric skull and the developmental patterns of the pediatric skull with aging. These two components will be investigated through the remainder of this thesis. The intended collective outcome of each of these components was to enable further insights into pediatric skull research, facilitating improvements in areas including pediatric cranial modeling and craniofacial surgery moving forward.

PART I: MICROSTRUCTURAL AND MECHANICAL ANALYSIS OF PEDIATRIC CRANIAL BONE

Understanding the microstructural and mechanical properties of pediatric cranial bone is critical towards developing craniofacial surgical hardware, materials, and procedures that are optimally suited for the pediatric population. Despite these potential positive outcomes, the pediatric skull has not been extensively studied. No previous studies have attempted to understand and quantify the microstructural properties of pediatric cranial bone. Additionally, prior experimental efforts have been limited by both sample size and subject availability, with the vast majority of test specimens coming from the neonatal age group. This limits their applicability to the wider pediatric population due to known structural and behavioral differences between the two age groups. Analyzing pediatric cranial bone from a wider age range with consideration of microstructural properties can provide greater insight into its mechanical properties.

Chapters 3-5 outline the microstructural and mechanical analysis of pediatric cranial bone that was done in this study. Chapter 3 covers the preparation process for pediatric cranial bone samples used in the study. Chapter 4 outlines the microstructural analysis approach that was implemented using the collected samples. Finally, Chapter 5 describes the experimental testing process that was employed as well as the mechanical properties that were determined for the samples of pediatric cranial bone. The enhanced microstructural and mechanical properties found from this study will facilitate improvements in current craniofacial surgical technologies for the pediatric population, improving long-term surgical outcomes moving forward.

CHAPTER 3: PEDIATRIC CRANIAL BONE SPECIMEN COLLECTION AND PREPARATION

To appropriately evaluate the mechanical and microstructural properties of the pediatric skull, experimental test samples must be procured from pediatric cranial bone specimens. This chapter outlines the process of acquiring pediatric cranial bone specimens and converting them into individual samples for microstructural and mechanical analysis processes.

3.1. Specimen Acquisition

Fresh pediatric cranial bone specimens were obtained as discarded surgical tissue from pediatric sagittal craniosynostosis corrective surgeries performed at the University of Virginia Medical Center. All specimens were obtained through a protocol approved by the University of Virginia Institutional Review Board for Health Sciences Research (IRB-HSR# 21137: Defining the Mechanical Properties of Pediatric Cranial Bone). Specimens were obtained from subjects ranging from four to ten months of age. Whole specimens, which consisted of a section of the left and right parietal bone and sagittal suture (typically 6 cm x 12 cm through the thickness of the bone) were kept fresh in a refrigerator (+5°C) prior to preparation and subsequent microstructural analysis and mechanical testing.

3.2. Sample Preparation

Test samples were acquired from the left and right parietal bones of each specimen in an orientation parallel to the sagittal suture, which was prematurely fused in the craniosynostosis patients. Since fused suture is known to thicken the bone beyond the thickness of normal surrounding bone, samples were acquired with a sufficient offset from the suture to avoid abnormalities and associated variations in bone morphology as compared to unaffected cranial bone.

During the preparation process, outlined in Figure 3-1, the bone was kept moistened with a saline solution. Individual samples were cut using bone scissors so that their dimensions were approximately 30 mm in length and 5 mm in width through the thickness of the bone, preserving all cross-sectional geometric features. The locations of each bone sample on the skull sample were noted for potential association with any location-based effects and sample size was chosen to maximize the number of samples obtained from each specimen.



Figure 3-1: Outline of the sample acquisition process for each specimen. Samples were acquired parallel to the sagittal suture, with the specific number depending on the size of the specimen.

After preparing individual samples from the larger cranial bone specimen, the ends of each sample were fixed into hollowed cubic ABS plastic end caps, shown in Figure 3-2, using a two-part epoxy resin (J-B Weld, Sulphur Springs, Texas) to give a gauge length of approximately 10 mm.



Figure 3-2: Each sample (green) was fixed within plastic end caps (purple) which were aligned with the micro-CT scan direction to correlate measured microstructural properties with the loading axis used during experimental testing.

To ensure that the sample was properly oriented within the end caps for mechanical testing and microstructural analysis, it was essential that the sample end caps were aligned with one another. Proper sample alignment was necessary for both microstructural analysis and experimental testing processes. For microstructural analysis, alignment of the end caps ensured acquisition of micro-CT images perpendicular to the gauge length of the test sample, as described in Chapter 4. For mechanical testing, end cap alignment ensured smooth displacement of the loading head and corresponding rotation of the bending fixture arms, as described in Chapter 5. Additionally, alignment also prevented excessive rotation of the contact points to ensure a nearconstant moment across the sample during testing.

To allow for proper sample alignment, a fixture was developed to align the sample while the epoxy cured (Figure 3-3). By securely fitting the sample end caps into the fixture bases and then attaching the side pieces to align them during the curing process, samples were able to dry with a straightened configuration and a consistent gauge length, ensuring microstructural analysis and mechanical testing could be appropriately performed.



Figure 3-3: The sample alignment fixture involved fitting end caps (purple) into the fixture base pieces (gray) and then attaching side pieces (red) to align the end caps while the epoxy cured.

After curing, bone samples were removed from the sample alignment fixture and wrapped in saline-moistened gauze. They were then stored in a refrigerator (+5°C) for future microstructural analysis and mechanical testing.

3.3. Sample Preparation Summary

Pediatric cranial bone specimens were obtained from craniosynostosis surgical procedures. They consisted of sections left and right parietal bone along with the sagittal suture, which was fused as a result of this condition. Individual pediatric cranial bone samples were prepared from these larger specimens with sufficient offset to avoid undesired effects from the fused suture. Once sized, samples were affixed within end caps which were aligned with one another. This ensured compatibility for future testing and analysis processes.

CHAPTER 4: MICROSTRUCTURAL ANALYSIS OF PEDIATRIC CRANIAL BONE

It is known that pediatric cranial bone exists as a single cortical layer at birth and transitions to a tri-layer structure with inner and outer cortical layers and a center diploe layer during the first few months of life. While the general microstructural characteristics of pediatric cranial bone are understood, they have not been explicitly quantified in prior studies. Rigorously quantifying the microstructural characteristics of pediatric cranial bone provides insight into its cross-sectional features, which is useful for enhanced calculations of mechanical properties. By facilitating an improved understanding of its response under loading, microstructural analysis of pediatric cranial bone enables development of technologies such as craniofacial surgical hardware which are optimally compatible with the pediatric cranial bone structure, ensuring the best long-term outcomes are met.

This chapter outlines the microstructural analysis process for pediatric cranial bone samples. This involved performing micro computed tomography (micro-CT) scans on samples, developing an algorithm to analyze the micro-CT scan results, and employing that algorithm to understand sample geometric properties and microstructure. The outcome of this chapter is an improved understanding and quantification of the microstructural and geometric properties of pediatric cranial bone.

4.1. Micro-CT Background

To visualize microstructural features of pediatric cranial bone samples, micro-CT was used. Micro-CT is a 3D imaging technique that uses X-rays to capture slice-by-slice images through an object's cross section (Microphotonics). This technique works by passing X-rays from a source through a sample and recording X-ray transmission through the sample with a detector as a two-dimensional projection (Figure 4-1) (Microphotonics). This process is repeated as the sample is rotated, and the collection of two-dimensional projections is reconstructed into a threedimensional representation of the structure of the object (Microphotonics). The benefit of using micro-CT to image pediatric cranial bone samples prior to testing is that it provides high resolution (micron-level) three-dimensional imaging of the interior structure of samples while not impacting the samples in any way (Microphotonics). In doing this, bone sample microstructural features can be studied prior to testing while the sample is in its original state and has not been impacted by experimental testing.



Figure 4-1: Micro-CT involves passing X-rays through a sample and measuring them with a detector as the sample is rotated. Projections are combined to produce a 3D image of the sample.

4.2. Performing Micro-CT on Pediatric Cranial Bone Samples

After preparation, test samples were removed from refrigeration and inserted into tubes for micro-CT (SCANCO Medical, Brüttisellen, Switzerland). Samples were scanned using a 10.5 μ m voxel resolution to characterize the local tissue microstructure and to calculate geometric properties for determination of mechanical properties.

To ensure appropriate calculation of geometric properties, it was necessary to ensure that samples were properly aligned with the axis of this micro-CT scan. This was done so that micro-CT scans could be performed perpendicular to the gauge length of the sample, as defined in Figure 3-2. Since samples were prepared so that the end caps could be aligned with the loading axis during experimental testing, this micro-CT images perpendicular to the gauge length could be captured by aligning the end caps with the micro-CT scan direction. Once properly aligned within the scanning tubes, micro-CT scans were performed on each sample. While the pre-test scans were used to determine geometric properties, as described in the following section, pre- and posttest scans were conducted on each sample.

Sample scans were output as a series of DICOM images, and each DICOM image set was processed as outlined in the following section.

4.3. Leveraging Micro-CT to Characterize Microstructure

A custom designed MATLAB function was developed to process micro-CT data for each sample and to analyze the corresponding structural morphology. After conducting micro-CT scans on each sample, DICOM images capturing transverse cross sectional geometry information were generated along the gauge length of each sample, with the gauge length defined as the region of the sample between the plastic end caps, as outlined in Figure 3-3 above. The structural analysis algorithm was then used to process each of these DICOM images to determine overall sample structural properties.

Prior to scanning, care was taken to ensure that the transverse axis of the sample was aligned with the scan direction. This was critical to calculate cross-sectional parameters perpendicular to the loading axis of the sample which is needed to appropriately calculate mechanical properties. Despite the alignment of the transverse axis with the scan direction, samples tended to be rotated so that the loading axis was not vertical within the DICOM image. To account for this, the function rotated each DICOM image by a set amount, which was found by determining the angle needed to rotate the original DICOM image so that the side edge of the plastic sample end holder is vertical in the image frame (Figure 4-2). After rotating DICOMs to align them with the direction of loading, images were then cropped to eliminate the likelihood of noise in the subsequent thresholding process.



Figure 4-2: DICOM images were rotated to align each sample with the direction of loading. This enabled accurate calculation of microstructural properties.

DICOM image pixels represent intensity values. Bone can be isolated within these images by targeting a specific range of intensities. It was specifically found that for these samples, bone possessed an intensity of greater than 1E4 based on the system used. Therefore, the initial thresholding process isolated bone pixels by thresholding on this value, where all pixels above the threshold were assigned "1" corresponding to bone and all pixels below the threshold were assigned "0" corresponding to a non-bone region (Figure 4-3).



Figure 4-3: DICOM images were thresholded to isolate bone cross-sections from surrounding material.

While the threshold process based on pixel intensity was fairly effective at isolating bone in each DICOM, there were errant pixels in each image that did not correspond to bone and therefore negatively affected the calculation of structural properties. The first step to remove errant pixels involved eliminating pixels outside the range of the bone sample within the image. This method summed the bone pixels in each row and column and eliminated any rows or columns with fewer than three bone pixels, allowing errant noise to be removed. Next, the edges of the bone sample were determined based on the sums of these bone pixels in each row and column, and all additional pixels outside of the determined sample edges were removed. The final step in the errant pixel removal process involved looking at each pixel in the DICOM image and, if that pixel had no surrounding neighbors within one or two pixels offset from its location, it was removed. This final step was repeated to remove any errant pixels that remained after the first cycle. After completing these procedures, the DICOM images were sufficiently thresholded to remove any errant pixels so that the structural properties could be accurately calculated.

Once cropped and thresholded, variables are initialized and DICOMs are individually analyzed along the sample gauge length to determine the different structural parameters. The structural parameters determined for each DICOM image are centroid, center of mass, area moment of inertia, and distance from the centroid to the top and bottom edges of the sample. The iterative calculation methodology used to calculate each of these parameters is presented in the Structural Measurement and Analysis section that follows. Following the equations presented in that section, the function steps through the image and tabulates the parameters for each boneassociated pixel. Once calculated, these structural properties were stored for each DICOM image and used to determine effective structural properties. These structural properties can then be used to calculate mechanical properties after preparation, testing, and analysis of pediatric cranial bone specimens, which will be outlined in the following section.

4.4. Geometric Properties

Cross-sectional sample geometry was determined by leveraging micro-CT scan DICOM images which were acquired transverse to the long axis of each sample, as described in Section 4.2 above. The custom-designed MATLAB script outlined in Section 4.3 was used to process DICOM images by calculating geometric properties individually for each cross-sectional slice. After thresholding images to isolate bone tissue, the centroid of each slice was determined using the following relation for each of n pixels in the slice corresponding to bone tissue:

$$\bar{y} = \frac{\sum_{i=1}^{n} y_i A_i}{\sum_{i=1}^{n} A_i}$$
(4-1)

Where \bar{y} is the vertical coordinate of the centroid of the slice, y_i is the vertical location of the specific pixel containing bone tissue, and A_i is the area of that pixel (Figure 4-4a).

From the vertical coordinate of the centroid for a given slice, the distance to the sample top and bottom edges was determined across the width of the corresponding slice. The distance, c, to the sample surface was determined as the 95th percentile of all values of c across the sample surface for the given slice (Figure 4-4a).

Finally, the second area moment of inertia, I_{zz} , was calculated for each slice using the following relation for each of the *n* pixels in the slice corresponding to bone tissue:

$$I_{zz} = \sum_{i=1}^{n} [I_i + A_i (y_i - \bar{y})^2] \quad (4-2)$$

Where I_{zz} is the second area moment of inertia in the direction of the bending axis, I_i is the moment of inertia of an individual pixel about its center, A_i is the area of the pixel corresponding to bone tissue, and y_i and \overline{y} defined above as the vertical pixel location and the vertical centroid coordinate, respectively.



Figure 4-4: a) Micro-CT DICOM image for a cross-sectional sample slice showing the centroid (denoted by the star) and the 95th percentile distance from the centroid to the sample surface (denoted as c) used for geometric property calculation. b) Measured length, L, corresponded to the gauge length of the sample. c) Measured bending angle, θ , corresponded to the average rotation angle of each of the two end fixtures from their original orientations.

In addition to calculating geometric properties through micro-CT analysis, properties were also calculated assuming a solid, uniform rectangular cross-sectional area to investigate its effect on measured stress and elastic modulus. This assumption of solid cross-section was employed in prior experimental studies.

4.5. Microstructural Property Results

Pediatric parietal skull bone was tested to failure under four-point bending (n = 68 specimens, 7 to 12 samples per specimen) at a strain rate of approximately 0.064 sec⁻¹. For each tested sample, both geometric and mechanical properties were measured and assessed both within and between test specimens. Measured geometric properties included thickness, width, and moment of inertia calculated about the bending axis.

For this study, there were two methods to calculate moment of inertia: 1) using micro-CT data to derive moment of inertia from the microstructural features (Equation 4-2), and 2) assuming a solid, rectangular cross-section of uniform width and thickness which was the approach used in

prior studies in the literature (Table 2-1). Comparing differences in moment of inertia calculation method using a paired t-test, micro-CT-calculated moment of inertia was significantly smaller than solid-approximated moment of inertia (p=0.002). These significant differences in calculation approach impact the corresponding stress and modulus measurements samples. Since it does not consider void spaces in the sample cross-section, the solid approximation approach results in an overestimation of the cross-sectional moment of inertia and a corresponding underestimation of the effective property when compared to the micro-CT calculation approach which accounts for these void spaces.

		Thic	kness	Bending MOI/Width (mm³)				<u>Micro-</u>
		<u>(mm)</u>		Solid		Micro-CT		<u>CT/Solid</u>
				Assumption		Calculation		<u>MOI Ratio</u>
Specimen Age	# Samples	Mean SD		Mean	SD	Mean	SD	Mean
4 mos	8	2.01	0.48	0.77	0.49	0.32	0.16	0.47
4 mos	9	2.37	0.40	1.20	0.64	0.54	0.29	0.47
5 mos	8	2.74	0.42	1.83	0.90	0.96	0.42	0.54
5 mos	7	1.58	0.56	0.43	0.38	0.17	0.12	0.45
6 mos	8	1.81	0.57	0.62	0.52	0.27	0.20	0.51
8 mos	9	2.05	0.17	0.73	0.20	0.45	0.12	0.62
10 mos	12	2.03	0.25	0.72	0.23	0.45	0.15	0.64
10 mos	7	1.21	0.38	0.19	0.22	0.08	0.08	0.46
Combined	68	2.00	0.41	0.83	0.49	0.42	0.22	0.53

Table 4-1: Geometric properties for measured pediatric cranial bone specimens.

Individual Test Specimens

Comparing individual samples for each test specimens, for the majority of specimens tested, individual sample geometric properties did not correlate with location on the specimen. For some specimens, however, samples prepared from the anterior portion of the specimen exhibited thinner cross-sections and smaller width-normalized moments of inertia than samples prepared from the posterior portion of the specimen; however, this location-based difference did not trend with specimen age and was only significant for a single specimen (Table 4-2).

	Mea	n Thickness	(mm)	Mean Bending MOI / Width (mm ³)				
Specimen Age	Anterior	Posterior	P-Value	Anterior	Posterior	P-Value		
4 mos	2.03	2.03	0.979	0.43	0.48	0.635		
4 mos	1.35	2.26	0.008	0.14	0.41	0.046		
5 mos	1.24	1.84	0.182	0.08	0.23	0.082		
5 mos	2.15	2.65	0.053	0.39	0.71	0.105		
6 mos	2.47	3.02	0.053	0.70	1.23	0.067		
8 mos	1.99	2.02	0.931	0.33	0.32	0.927		
10 mos	1.08	1.55	0.143	0.05	0.16	0.114		
10 mos	1.91	2.12	0.094	0.38	0.48	0.227		

Table 4-2: Geometric properties for individual pediatric cranial bone specimen samplesseparated by location on the specimen. P-values denote sample location-based significance foreach geometric property by test specimen.

All Test Specimens

One-way Analysis of Variance (ANOVA) tests across all test specimens for thickness and width-normalized moment of inertia indicated significant differences were present between specimens (p<0.001 for each parameter), though these differences did not appreciably trend with specimen age, as seen in Figure 4-5.



Figure 4-5: Thickness (a) and width-normalized moment of inertia (b) versus age plots for each test sample demonstrate no definitive trend of properties with specimen age.

4.6. Microstructural Analysis Discussion

In this study, micro-CT was performed to enhance understanding of pediatric skull microstructure and to consequently better inform mechanical property measurements. Prior

studies involving cranial bone samples utilized geometric measurements of whole-bone crosssectional geometry such as width and thickness to calculate the second area moment of inertia, and Euler beam analysis was used to calculate the corresponding mechanical properties. While this measurement approach was relatively straightforward and the results provide effective property measurements that can be implemented into finite element models or similar tools, it did not account for the non-uniform cross sections seen within cranial bone possessing a tri-layer structure. To provide microstructural-level insights by accounting for this non-uniform cross-sectional geometry when measuring geometric properties, this study performed micro-CT scans on each tested sample. Using a custom MATLAB script, each micro-CT image frame was analyzed and corresponding geometric properties (e.g., area moment of inertia, centroid, thickness) were calculated using a voxel-based approach. Average geometric properties for all frames in the sample gauge length were then used to calculate effective mechanical properties of the sample using an Euler beam approach similar to that employed in prior studies.

Comparing the second area moment of inertia of the micro-CT-calculated cross section and the corresponding solid-approximated cross-section, the moment of inertia of the micro-CT-measured cross section was consistently smaller since it accounts for porosities within the bone structure. Across all tested samples, the ratio of the micro-CT-calculated and solid-approximated moments of inertia for the same sample was approximately 0.5 (Table 1). Assuming an idealized tri-layer rectangular cross-section with solid, rectangular upper and lower cortical tables of identical thickness and a center non-structural diploe layer, this ratio of 0.5 suggests that nearly 80% of the cross-section was non-structural.

For the solid-approximated sample analysis approach, the consequence of neglecting the non-structural space within the cross section was a larger moment of inertia and a correspondingly

smaller calculated stress and elastic modulus as compared to the micro-CT-based analysis method, with the ratio between the two calculated stresses and elastic moduli being the same as the micro-CT/solid moment of inertia ratio for the particular sample. By using micro-CT to analyze cross-sectional geometry, a more accurate microstructure-level representation of geometric properties throughout the sample points towards potentially enhanced mechanical property measurements for each tested sample.

4.7. Microstructural Analysis Summary

Pediatric cranial bone microstructural properties were quantified for 68 total samples obtained from eight test specimens ranging in age from 4 to 10 months. To do this, samples were scanned using micro-CT and a custom-designed analysis algorithm was developed using MATLAB to analyze the scans to determine microstructural properties. It was found that geometric properties did not trend with location within a single specimen or with age across all specimens. Additionally, comparing the moment of inertia calculated using microstructural analysis to that calculated assuming a solid cross-section, the approach employed in prior studies, the value was approximately half, suggesting nearly 80% of the cross-sectional structure is non-structural. Using these microstructural alongside experimental testing results, enhanced mechanical properties can be obtained that can be understood in the context of the entirety of test samples both from this study and from prior experimental results.

CHAPTER 5: MECHANICAL TESTING OF PEDIATRIC CRANIAL BONE

It is understood that pediatric cranial bone exhibits lower stiffness and greater flexibility than adult cranial bone under loading because the compliance of pediatric skull tissue allows for the growth of the brain; however, there is a paucity of available experimental data to meaningfully understand these differences. While experimental data for adult cranial bone under loading exists for a variety of loading applications including tension, compression, shear, and bending, there is a noticeable lack of available data for the pediatric population, with the bulk of prior experimental efforts concentrated towards the neonatal age range. Additionally, since prior experimental studies have not considered microstructural characteristics of the underlying cranial bone when assessing mechanical properties, their findings were likely not truly indicative of the true tissue response. Therefore, to facilitate improved pediatric craniofacial surgical technologies, experimental testing of pediatric cranial bone samples along with previously measured microstructural properties will be used to provide greater insight into the mechanical behavior of the pediatric skull.

This chapter outlines the experimental testing process for pediatric cranial bone samples. This involved developing a test rig and four-point bending device to test pediatric cranial bone samples, using the results of experimental tests alongside microstructural property findings to determine mechanical properties of pediatric cranial bone samples, and understanding mechanical properties in light of currently available data. The outcome of this chapter is a greater understanding of the mechanical properties of pediatric cranial bone.

5.1. Four-Point Bending Rig Development

Due to the low failure forces of pediatric skull bone in combination with its high levels of compliancy, existing available experimental test devices at the Center for Applied Biomechanics were not appropriate due to limitations associated with loading force resolution or available stroke length. Therefore, to mechanically test pediatric cranial bone to effectively evaluate its loading response, a custom test rig was needed (Figure 5-1). This test rig, which required both a high control resolution and a large stroke length, consisted of two primary components: a base component, which consisted of an aluminum frame and a linear actuator-driven loading head, and a four-point bending fixture, which was specifically designed to test pediatric bone samples. Both the base component and the four-point bending fixture were developed and refined using SolidWorks (Dassault Systemes, France). After developing each component of the test rig, the base was fabricated in-house at the University of Virginia Center for Applied Biomechanics and the components of the four-point bending setup were 3D-printed out of carbon fiber-embedded Onyx material (Markforged Mark Two, Markforged, Inc, Watertown, MA). While the bending fixture was developed specifically for this test series, the base component was designed to be usable for a wide range of mechanical tests. To enable this interchangeability, the bending fixture was made to be removable from the base component by screwing into an adapter plate which was then bolted to the frame. Similarly, associated measurement instrumentation, such as load cells or potentiometers, could also be added to the base using adapter plates containing the specific thread patterns of the instruments.



Figure 5-1: A schematic of the entire experimental test setup (a) with a zoomed view of the fourpoint bending test design (b) and a photograph of the fabricated setup containing specific test fixtures and instrumentation (c).

The test rig was controlled using an Arduino microcontroller (Arduino, Somerville, MA) which was operated via MATLAB (Mathworks, Natick, MA). Specific test rig parameters that could be controlled were the rate and the magnitude of displacement of the linear actuator. The four-point bending fixture designed for pediatric skull bone tests translated the downward displacement of the loading head attached to the linear actuator into bending action on the sample (Figure 5-2). Using Euler beam analysis, as outlined later in this chapter, the force associated with bending and the corresponding bending angle were translated into stress and strain, respectively, for determination of loading behavior.

5.2. Mechanical Testing Procedure

As outlined in Chapter 4, micro-CT scans were conducted prior to experimental testing to quantify microstructural and geometric properties for each sample. After scanning, samples were inserted into a custom-designed four-point bending apparatus which is described in greater detail below. Once inserted into the bending apparatus, the test setup was aligned so that the sample was centered between the end supports and the loading head was centered above the sample. The apparatus employed roller bearings as supports to minimize friction effects and a ball-and-socket loading head to allow for free rotation of the loading head to ensure constant contact with the setup and a corresponding near-constant moment across the sample.



Figure 5-2: From the initial configuration of the four-point bending setup for samples (left), downward displacement of the loading head resulted in sample bending to failure (right).

Displacement-controlled failure tests were run on samples through prescribed displacement of the loading head. The loading head was driven by a linear actuator at a displacement rate of 7.6 mm/s, which corresponded to a strain rate of approximately 0.064 s⁻¹ since strain was related to the bending angle of the sample. Downward displacement of the loading head corresponded to bending of the sample to failure. Force for each test was measured using a Honeywell Model 31 222.4 N single-axis load cell (Morristown, New Jersey) and high definition video of each test was recorded at a frame rate of 120 frames/sec for strain measurement using a Edgertronic Model SC1 video camera (Sanstreak Corporation, San Jose, California).

5.3. Mechanical Properties

For mechanical property calculations for each sample, the micro-CT distance to the sample surface (c) and average area moment of inertia (I_{zz}) were employed along with Euler beam analysis. To apply Euler beam analysis, the calculation approach used for mechanical properties employs a simplified assumption that the bone exists as a homogeneous cross section. This leads to mechanical property information corresponding to the average loading response of the samples which provides effective mechanical property measurements for each sample. Additionally, in accordance with Euler beam analysis, it was assumed that cross-sections remain perpendicular to the bending axis throughout testing and that sample bending angles are small.

Using Euler beam assumptions in combination with determined geometric properties, stress, σ , was estimated throughout the test duration using the equation:

$$\sigma(t) = \frac{M_z(t)c}{l_{zz}}$$
(5-1)
$$M_z(t) = \frac{F_z(t)k}{2}$$
(5-2)

Where σ is the stress and M_z is the bending moment across the sample determined from the load cell force reading, F_z , and the distance between the contact points above and below the end supports on either side of the sample, *k* (Equation 5-2).

Also using Euler beam assumptions, strain, ε , was estimated as a function of time utilizing the displacement of the loading head for the outer surface of the bone samples during testing. This was done by employing video tracking data corresponding to the rotation of the sample end pieces using the equation:

$$\varepsilon(t) = \frac{2c\theta(t)}{L} \tag{5-3}$$

Where θ is the average angle of rotation of the two ends of the sample, and *L* is the gauge length of the sample (Figure 4-4b and 4-4c).

Since experimental tests indicated that samples exhibited a continuous yielding behavior prior to failure, a Ramberg-Osgood model consisting of a piecewise linear and power law representation of strain in terms of stress was fit to the data. This was done using MATLAB's Curve Fitting Toolbox with a Nonlinear Least-Squares fitting method. The Ramberg-Osgood stress-strain relationship follows the form:

$$\varepsilon(\sigma) = \frac{\sigma}{E} + \left(\frac{\sigma}{H}\right)^n$$
 (5-4)

Where ε is the strain, σ is the stress, *E* is the initial modulus of elasticity, and *E*, *H*, and *n* are the fitted parameters. To avoid potential overfitting issues for this relationship, the initial modulus of elasticity was obtained from the stress-strain data using a cutoff region of 10% of the ultimate strain for linearity prior to fitting the *H* and *n* parameters, which depend on the yielding characteristics of the sample.

5.4. Results

Pediatric parietal skull bone was tested to failure under four-point bending (n = 68 specimens, 7 to 12 samples per specimen) at a strain rate of approximately 0.064 sec⁻¹. For each tested sample, mechanical properties were assessed both within and between test specimens. Ultimate stress and strain, initial elastic modulus, as well as Ramberg-Osgood model parameters were determined for each sample (Figure 5-3).



Figure 5-3: Stress-strain curve from a typical bending test with overlaid measured ultimate stress and strain and fitted Ramberg-Osgood model.

5.4.1. General Loading Behavior

Across all mechanical tests, a continuous reduction in stiffness prior to ultimate stress and sample failure was observed. Consequently, the elastic modulus calculated for samples was determined from the initial region of stress-strain curves. The Ramberg-Osgood piecewise linear and power law model was fitted to the stress-strain response obtained from each mechanical test (R^2 >0.87 for each fit), and average parameters were calculated for each test specimen (Figure 5-4). Additionally, in Figures 5-5 and 5-6, these average curves are plotted alongside each mechanical test for individual test specimens. These figures demonstrate that, despite the inherent sample-to-sample variability, the average Ramberg-Osgood model fits provide a good representation of each specimen's loading response.



Figure 5-4: Ramberg-Osgood model fits of stress-strain responses for each specimen across all individual samples. Each curve demonstrates a continued reduction in stiffness prior to reaching sample failure indicative of a Ramberg-Osgood model response.



Stress vs. Strain Response for All Test Samples by Specimen (1-4)

Figure 5-5: Average specimen Ramberg-Osgood model fits for Specimens 1-4 (seen as black dashed curves) up to mean specimen ultimate stress plotted alongside stress-strain responses for all individual specimen samples shows appropriate representation of average specimen response.



Stress vs. Strain Response for All Test Samples by Specimen (5-8)

Figure 5-6: Average specimen Ramberg-Osgood model fits for Specimens 5-8 (seen as black dashed curves) up to mean specimen ultimate stress plotted alongside stress-strain responses for all individual specimen samples shows appropriate representation of average specimen response.

5.4.2. Individual Test Specimens

Comparing individual samples for each test specimen, no clear trends in ultimate behavior or elastic modulus were present with respect to location on the specimen (Table 5-1). In general, samples with smaller moments of inertia tended to fail at lower forces than those with larger moments of inertia, resulting in generally comparable values for effective ultimate stresses for samples from each test specimen (Figure 5-7a). Similarly, samples with thinner cross-sections tended to fail at greater bending angles than those with thicker cross-sections, corresponding to comparable effective ultimate strains for samples from the same test specimen (Figure 5-7b).

	M	odulus (<u>GPa)</u>	Ultim	ate Stra	<u>in (%)</u>	Ultimate Stress (MPa)			
Specimen Age	Ant.	Post.	P-Val	Ant.	Post.	P-Val	Ant.	Post.	P-Val	
4 mos	2.85	3.68	0.128	7.52	6.89	0.520	89.97	116.97	0.028	
4 mos	7.06	3.81	0.068	4.98	7.06	0.112	101.68	92.96	0.449	
5 mos	4.93	3.77	0.620	7.43	6.43	0.695	92.50	81.77	0.680	
5 mos	2.95	2.60	0.581	7.52	7.76	0.891	84.93	86.93	0.839	
6 mos	2.58	1.93	0.031	7.04	7.98	0.507	59.13	65.29	0.583	
8 mos	5.25	6.19	0.621	6.20	4.14	0.022	108.32	88.07	0.517	
10 mos	6.95	5.17	0.044	5.27	7.19	0.279	113.31	84.49	0.307	
10 mos	5.49	3.68	0.016	6.34	7.02	0.647	101.59	100.45	0.924	

Table 5-1: Mechanical properties for individual pediatric cranial bone specimen samples separated by location on the specimen (anterior and posterior portions). P-values denote sample location-based significance for each mechanical property by test specimen.



Figure 5-7: (a) Sample failure force as a function of width-normalized moment of inertia demonstrates an increasing trend across all test samples, while (b) sample failure bending angle as a function of thickness demonstrates a decreasing trend across all test samples.

5.4.3. All Test Specimens

Effective ultimate properties and Ramberg-Osgood parameters, including initial elastic moduli, for each test specimen are presented in Table 5-2. One-way ANOVA tests for each 54

average Ramberg-Osgood parameter (*E*, *H*, and *n*) and ultimate property (strain and stress) indicated significant differences exist between specimens (p<0.001 for each); however, differences did not vary according to specimen age (Figure 5-8). Average specimen Ramberg-Osgood fit parameters ranged from 2.3GPa to 6.4GPa for *E*, 4.0GPa to 7.2GPa for *H*, and 2.6 to 4.1 for *n*. Across all specimens, average ultimate strains ranged from 5.17% to 7.63% and average ultimate stresses ranged from 62.2MPa to 105.1MPa (Table 5-2).

		Ramberg-Osgood Parameters						Ultimate Values			
		E (GPa)		H (GPa)		n		Strain (%)		Stress (MPa)	
Age (mos)	Samples	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
4	8	5.72	2.41	7.19	2.98	3.73	1.23	5.17	1.40	98.19	39.97
4	9	2.79	0.88	5.63	1.57	4.05	2.96	7.63	2.39	85.82	13.26
5	8	2.25	0.46	3.99	1.28	3.18	0.75	7.51	1.81	62.21	14.31
5	7	4.27	2.70	5.14	2.01	2.97	1.01	6.86	2.91	86.37	29.85
6	8	5.44	2.58	6.74	1.44	3.76	1.12	6.02	1.84	97.32	14.84
8	9	4.28	1.18	6.15	1.14	2.63	0.69	6.79	1.91	100.83	15.17
10	12	3.27	0.94	7.00	1.79	3.42	1.33	7.20	1.59	103.47	22.40
10	7	6.44	1.13	7.12	2.65	3.85	1.47	5.82	1.97	105.08	31.02
Combined	68	4.19	2.09	6.17	2.09	3.44	1.49	6.68	2.05	92.99	26.10

Table 5-2: Summary of Effective Mechanical Properties for Each Specimen



Figure 5-8: Modulus (a), ultimate strain (b), and ultimate stress (c) versus age plots for each test sample demonstrate no definitive trends of properties with specimen age.

5.5. Experimental Testing Discussion

With a lack of widely available material property data, it was necessary to perform mechanical testing on pediatric skull tissue to better understand how the pediatric skull behaves under loading to improve both current surgical treatment methodologies and surgical hardware used for the pediatric population. In this study, mechanical testing on pediatric skull parietal bone tissue was performed to contribute to this limited knowledge base.

5.5.1. Four-Point vs. Three-Point Bending

Most prior studies involving cranial bone samples have used three-point bending methods. While this test method is simple to configure and measure, it has several inherent drawbacks relating to the loading scenario. In the three-point bending setup, the tested sample is subjected to a shear force throughout the sample that is proportional to the magnitude of the load which may result in unintended loading effects. The bending moment is non-constant, and results in the maximum stress being concentrated at the point of force application, which causes the loading behavior to be sensitive to the localized cross-sectional bone structure at this location. Finally, with a force applied directly on the sample surface, it can be difficult to distinguish between failure due to the force magnitude or due to stress concentrations resulting from contact with the sample surface. As a result of these potential consequences, three-point bending tests are often best suited for homogeneous materials.

Due to the potentially undesired effects associated with three-point bending and because of the nonhomogeneous cross-sectional geometry of cranial bone, the tests in this study utilized a four-point bending design. The benefits of this experimental design is the constant moment applied across the entire tests sample and the absence of shear forces on the sample and a constant moment present across the sample. Furthermore, the point loads applied to the system do not have
to be located on the tissue itself, which removes the complicating stress concentration at the point of contact. This allows for a better understanding of the effective test sample loading response as a whole compared to that afforded by a three-point bending setup.

Since the irregularities in cranial sample geometry could have prevented uniform contact throughout the test duration, the four-point design used in this study featured a ball-and-socket joint between the loading head and the bending apparatus. The presence of this joint allowed for a rotational degree of freedom to ensure constantly maintained contact points with each end support throughout the duration of the test. By maintaining these constant points of contact, there were both negligible shear forces and a near-constant moment across the sample throughout the duration of testing, enabling the entire sample to be essentially equally affected by the loading scenario. Subjecting the entire sample to a similar loading scenario allowed for a better understanding of the sample as a whole which aided in measurement of effective loading behavior and mechanical properties.

5.5.2. Age-Related Effects

While it is known that mechanical properties vary with aging, this study found no significant differences among tested samples as a function of age for this population of test specimens, with ages ranging from 4 to 10 months. A possible explanation for this could be that the tested age range was too narrow to identify specific age-related differences. Additionally, within the age range tested, a large amount of inherent developmental and biological variability was present, which could contribute to the lack of an age-specific trend in mechanical properties. This was apparent through analysis of the micro-CT scans, with visible differences in cross-sectional morphology and associated geometric properties for the samples of each specimen which did not reflect any significant age-specific trends.

5.5.3. Comparison to Prior Studies

Ultimate Stress and Strain

Looking at the entire body of tested pediatric parietal bone parallel to the sagittal suture, very few prior studies tested samples within the 4-month to 10-month specimen age range of this study. Only Margulies and Thibault (2000) and Coats and Margulies (2006) tested samples that fell within this range, and their sample sizes within the age range were comparatively small (4 and 1 parietal bone samples, respectively, each from a single subject).

When considering micro-CT to calculate mechanical properties, greater metrics for ultimate stress and elastic modulus occur due to smaller moments of inertia. When assuming solid cross-sectional sample geometries, while the results of this study were generally consistent with those of Margulies and Thibault, they were greater that reported by Coats and Margulies. Additionally, when looking at the entire body of tested pediatric parietal bone parallel to the sagittal suture, there is a wide variation in reported ultimate stress and strain with aging. This could potentially be attributed inherent biological variability between specimens or to variations in testing procedures.

Elastic Modulus

Comparing the fitted initial elastic moduli from this study to those obtained from prior studies and accounting for differences in the moment of inertia calculation method employed, the values obtained from this study are generally comparable to the elastic moduli found in prior studies (Figure 5-9). While differences between values could be attributed to biological variability, it could also be due to differences in modulus calculation method. Other studies including Coats & Margulies (2006) and Margulies & Thibault (2000) were able to identify elastic regions in their experimental data and calculated moduli from these regions. Similar to this study, Davis et al. (2011) employed a Ramberg-Osgood model; however, they were able to identify a 0.2% yield offset in their experimental data to fit parameters for the power law portion of the model. Since

large amounts of strain were observed for samples in this study, the yield offset method was not deemed to be appropriate. Therefore, to avoid issues with overfitting model parameters, the initial elastic modulus was determined using a cutoff region of 10% of the ultimate strain for linearity, and the other Ramberg-Osgood parameters were then fit using the entire stress-strain response.



Figure 5-9: Comparison of parietal bone elastic moduli from this and prior studies testing specimens in the prenatal to 15-month age range.

Pediatric and Adult Comparison

When extending to the adult population and comparing ultimate stress and strain, specimens of this study exhibited lower elastic moduli (~3 times) slightly lower ultimate stresses (~10MPa) and considerably greater ultimate strains (~5 times) when comparing across all tested samples (Motherway et al. 2009). These differences between the pediatric and adult population likely point toward inherent changes in cranial composition, rigidity, and structure that occur with biological development.

5.6. Microstructural and Mechanical Analysis Overall Conclusions

Pediatric cranial bone obtained from subjects ranging from 4 to 10 months was tested under four-point bending. Micro-CT provided insight into tissue microstructure and cross-sectional geometric properties, with differences in using micro-CT and solid approximation approaches resulting in different mechanical property measurements. The results suggest that the mechanical properties of pediatric skull bone were different than those of adult bone, with elastic moduli roughly three times less, slight differences in ultimate stress, and ultimate strains roughly five times greater. The results of this study contribute to and build upon the limited knowledge base of pediatric cranial bone mechanical properties by increasing the number of specimens tested in the 4- to 10-month range and by incorporating a micro-CT analysis approach, which considers localized microstructure, to calculate geometric properties. By providing greater insight into the microstructural characteristics of pediatric cranial bone (Chapter 4) and by improving our understanding of the response of pediatric cranial bone under loading (Chapter 5), the findings of this study can be used to improve the efficacy of pediatric skull surgical hardware by incorporating materials that are compatible with the properties of pediatric cranial bone. Additionally, leveraging these results to understand the growth patterns of the aging skull can provide a useful tool to better inform surgical planning and treatment methodologies moving forward. This will be done in the following chapters through the development of a computational growth model of the pediatric skull.

PART II: DEVELOPMENT OF A PEDIATRIC SKULL COMPUTATIONAL GROWTH MODEL

While it is known that the pediatric skull grows rapidly during the initial stages of life, it is unknown what specific factors contribute to the observed growth and how those factors inform the underlying morphology of the developing skull. Prior studies have identified that both mechanical forces and genetic inputs combine to produce the observed skull morphology (Lee et al. 2019). In many instances, however, the genetic inputs are directly influenced by those mechanical forces. For the developing pediatric skull, mechanical forces arise from the expansion of the growing brain, which occurs at a noticeably rapid rate during the early stages of life. Expansion of the brain causes perturbations in the local cellular environment which signals cells to proliferate and differentiate, forming additional bone tissue which contributes to skull growth (Katsianou et al. 2016). The formation of additional bone tissue changes the shape and structure of the skull by altering its localized material properties and thickness over time.

Finite element models are important tools to investigate the response of biological models to the imposition of mechanical forces. Since pediatric skull growth occurs as a result of mechanical forces, FE modeling is a useful tool that can be leveraged to evaluate skull growth. Currently, however, no model has been developed to investigate the shape and structural changes of the pediatric skull that occur in response to the underlying mechanical forces imparted upon it by the growing brain.

Chapters 6-8 outline the development and preliminary assessment of a novel computational model that was developed to predict pediatric skull growth. As outlined in the following chapters, growth was modeled by expanding a pediatric cranial FE model over a set period of time through FE simulations within LS-DYNA. Individual simulations were run within corresponded to discrete periods of aging, and elements of the cranial FE model were individually grown following each simulation in response to the mechanical loading they experienced. Chapter 6 outlines the development of this growth methodology, which was done differently according to the physiological component represented by the element. Chapter 7 will implement this remodeling process within a pediatric skull FE model to simulate cranial growth with age. Finally, using the model developed in Chapters 6 and 7, Chapter 8 will perform a parametric analysis to assess the sensitivity of the model to a variety of input parameters to understand which are most important to consider for future model iterations moving forward; additionally, the model will be applied to understand its ability to predict growth patterns in response to a pathological morphology. Due to the lack of currently available data regarding the pediatric skull, the overall intended outcome of Chapters 6-8 was the development of a computational model of pediatric skull growth that is able to act as a platform for future growth models to build upon moving forward.

CHAPTER 6: DEVELOPMENT OF A TISSUE-SPECIFIC STRUCTURAL REMODELING PROCESS FOR PEDIATRIC SKULL GROWTH

In this chapter, an analytical model of pediatric skull tissue growth was developed with the intension of implementing it into each element of a whole pediatric skull model. The analytical model involved translating a mechanical stimulus into a tissue growth response affecting material stiffness and cross-sectional properties. Since it is understood that different anatomical components within the skull develop differently with aging, different update methodologies were required for each cranial tissue type to capture the observed physiological behaviors of each of these components when modeling skull growth. This was specifically done for bone, fontanelle, and suture tissue based on current physiological understanding and experimental data.

6.1. Use of Strain for Driving Tissue Growth

Physiologically, it has been found that bone growth occurs in response to external mechanical stimuli imposed upon the local bone environment (Weinans et al. 1992; Katsianou et al. 2019). These mechanical stimuli induce action by bone growth regulating cells including osteoblasts, osteoclasts, and osteocytes which cause local bone adaptations to occur (Katsianou et al. 2019). Different growth modeling approaches in the literature have employed different phenomenological metrics such as stress or strain to quantify the mechanical stimuli imparted upon the model to inform growth processes. For the growth model developed in this study, the chosen metric to inform bone growth in response to loading initiated by underlying brain tissue was maximum principal strain.

From a simplified standpoint, strain causes bone to remodel by updating its bending stiffness, which is the resistance of a structure against bending deformation. In the case of the developing skull, bending deformation occurs due to outward pressure from the brain during the cranial growth process. This assumption that cranial bone remodels its bending stiffness in response to bending deformation is based on the knowledge that during bending, the top and bottom surfaces of a loaded structure are under the greatest stress and strain. Understanding that cranial bone, like other biological structures, adapts to the loading conditions imposed upon it (Weinans et al. 1992), the cranial bone cross-section adjusts at its top and bottom surfaces to a greater extent, which is evidenced through the tri-layer cranial bone structure. The bending stiffness update is translated to growth within the model in two primary ways: material updates, which was imparted by increasing the tissue modulus, and cross-section updates, which was imparted by increasing the tissue thicken (and hereby increasing the moment of inertia).

In the case of the skull, the amount of strain experienced in the tissue is related to the bending deformation that occurs due to outward pressure from the brain during the cranial growth process. This strain response causes the tissue to remodel, and for this study, it is assumed that the remodeling process will affect the bending stiffness of the cranial tissue. Bending stiffness is the resistance of a structure against bending deformation, and using Euler beam theory, is represented as the product of the Young's modulus, E, and the moment of inertia, I (Equation 6-1).

Bending Stiffness = EI (6-1)

Thus, the bending stiffness update is translated to growth within the model in two primary ways: material updates, which were imparted by increasing the tissue modulus, and cross-section updates, which were imparted by increasing the tissue thickness (and hereby increasing the moment of inertia). Increases in both properties are observed in the developing skull.

6.2. Analytical Model of Bone Tissue Growth

Physiologically, at an early age, the dominant form of bone growth is stiffening, as layers of bone are deposited due to the high level of activity of osteocytes (Lee et al. 2019). By several

years of age, as the stiffness of bone tissue approaches that of adults, growth is primarily dominated by thickening of the bone (Davis et al. 2011). Using these fundamental observations, an analytical bone tissue growth model was developed.

The analytical model for bone tissue growth was based on updating its bending stiffness through adjustment of the tissue elastic modulus and tissue thickness. The extent to which these properties are updated depends on two components: the amount of strain the tissue is experiencing, and the current elastic modulus of the tissue. The overall magnitude of bending stiffness growth (ΔEI) depends solely on the strain present within the tissue (ε). But since bending stiffness is a function of modulus and moment of inertia, the proportion of the overall bending stiffness growth that is attributed to an update of the modulus (ΔE) and thickness (ΔI) will depend on the current state of the elastic modulus (E) of the tissue. Thus, the bone tissue update process contains two sequential steps. First, strain is evaluated to determine the tissue's magnitude of bending stiffness growth. Second, modulus is evaluated to assign the bending stiffness growth towards material and thickness growth. Each step will be described in detail in the following sections. A flow chart outlining the bone tissue update process is shown in Figure 6-1.



Figure 6-1: Flow chart of the bone tissue growth process outlining strain and modulus evaluation to determine bending stiffness and corresponding material and thickness growth.

6.2.1. Strain Evaluation to Determine Bone Tissue Growth Proportion (ΔEI)

The bone tissue bending stiffness growth proportion (ΔEI) depends on the strain within the tissue. The applied strain is assessed using a strain growth function consisting of two strain

thresholds, ε_{growth} and ε_{max} . ε_{growth} corresponds to the minimum strain threshold for which the tissue will be updated – for strains less than this value, no growth will occur. ε_{max} corresponds to the strain threshold at and beyond which the tissue will be updated a maximum amount, $\Delta EI_{max,bone}$. The use of ε_{max} ensures a limit on how much the tissue will be allowed to increase ΔEI , hereby preventing non-physiological growth. Bone tissue strains falling between the two strain thresholds will be assigned a bending stiffness update proportional to the maximum bending stiffness update amount, as described in Table 6-1 and seen graphically in Figure 6-2.

Table 6-1: Overall bone tissue growth, ΔEI , depends on its strain in relation to the predefined strain thresholds ε_{growth} and ε_{max} .

<u>Measured Strain (ε)</u>	<u>Update Proportion (Δ<i>EI</i>)</u>
$\varepsilon < \varepsilon_{growth}$	0
$\varepsilon_{growth} \leq \varepsilon < \varepsilon_{max}$	$\left(\frac{\Delta EI_{max,bone}}{\varepsilon_{max} - \varepsilon_{growth}}\right) * (\varepsilon - \varepsilon_{growth})$
$\varepsilon \geq \varepsilon_{max}$	$\Delta EI_{max,bone}$



Figure 6-2: Representation of the bone tissue bending stiffness update proportion, ΔEI , which is scaled linearly between 0 and $\Delta EI_{max,bone}$ based on maximum principal strain.

The maximum bending stiffness update amount, $\Delta EI_{max,bone}$, was determined using physiological data for both the elastic modulus and thickness of bone at the initial and final ages of the growth model (6-months and 2-years) as well as the number of steps in the simulated growth process (1.5 years, or 78 1-week steps). This approximates the expected proportion of bone tissue bending stiffness growth through combined skull stiffening and thickening that would occur for a single growth step between 6-months and 2-years of age assuming a constant linear increase in growth throughout that age span. A detailed calculation of this parameter is presented in Appendix B.

6.2.2. Modulus Evaluation to Determine Bone Tissue Material Growth (ΔE) and Thickness Growth (ΔI)

After determining the bone tissue's bending stiffness update magnitude, ΔEI , the proportion attributed between material growth, ΔE , and thickness growth, ΔI , must be determined. A coefficient, β , is used to assign the proportion of the increase in bending stiffness that is attributed to an increase in modulus. β ranges between 0 and 1, where $\beta = 1$ indicates that the increase in bending stiffness is solely attributed to an increase in modulus, and where $\beta = 0$ indicates that the increase in bending stiffness is solely attributed to an increase in thickness. To apply β towards updating material (ΔE) and thickness (ΔI), it is multiplied by the bending stiffness update proportion, ΔEI , according to Equations 6-2 and 6-3.

$$\Delta E = (\beta * \Delta EI) \tag{6-2}$$

$$\Delta I = ((1 - \beta) * \Delta EI) \tag{6-3}$$

The proportionality coefficient β is not predetermined or constant, but is a function of the tissue's current modulus in relation to the initial bone modulus at 6 months of age, E_0 , and the

modulus of a 6-year old, E_{max} . The initial modulus, E_0 , corresponds to the starting bone modulus for a 6-month old because growth at this age predominantly occurs through stiffening of the skull (Lee et al. 2019). Additionally, available pediatric biometric data does not demonstrate appreciable thickness variations between individuals within the first several months since birth (Crandall et al. 2013). The maximum modulus, E_{max} , corresponds to the average cranial bone modulus of an individual at 6 years of age because at this age, the modulus of the skull is close to that of an adult, and growth at this point in the aging process is predominantly attributed to increasing skull thickness, with biometric data suggesting greater cranial thicknesses for individuals at this age (Lee et al. 2019; Davis et al. 2011; Crandall et al. 2013). At each iteration of the growth process, the proportionality coefficient β was assigned a value based on a linear function between the E_0 and E_{max} , as summarized numerically in Table 6-2 and graphically in Figure 6-3 below.

Table 6-2: The β -parameter is scaled linearly between 0 and 1 based on the bone tissue modulus in comparison to the initial bone modulus, E_0 , and the maximum bone modulus, E_{max} . It assigns the bending stiffness update proportion, ΔEI , towards updating material (ΔE) or thickness (ΔI).

<u>Element Modulus</u> <u>(E)</u>	<u>Update Parameter</u> <u>(β)</u>	<u>Material Update</u> <u>(ΔE)</u>	<u>Thickness Update</u> <u>(ΔI)</u>
$E < E_0$	1	ΔEI	0
$E_0 \leq E < E_{max}$	$1 - \left(\frac{E - E_{6mos}}{E_{6yr} - E_{6mos}}\right)$	$\beta * \Delta EI$	$(1-\beta) * \Delta EI$
$E \geq E_{max}$	0	0	ΔEI



Figure 6-3: Graphic representation of the β -parameter, which is scaled linearly between 0 and 1 based on bone element modulus. This parameter assigns material and thickness growth components from the overall growth magnitude.

6.2.3. Applying Material and Thickness Growth to Bone Tissue

Once the specific material and thickness update parameters were determined, they were assigned to update the tissue modulus, E, and thickness, t, as proportions of their current values (Equations 6-4 and 6-5). Material growth was applied directly, while thickness growth was applied as a cubic factor of the thickness update, as described in Appendix C.

$$E_f = E_i * \Delta E \qquad (6-4)$$
$$t_f = t_i \sqrt[3]{\Delta I} \qquad (6-5)$$

Since the overall bending stiffness update proportion, ΔEI , was a function of strain, and the specific material (ΔE) and thickness (ΔI) update components were functions of both ΔEI and β , response contours for bone tissue growth were determined as functions of modulus and strain (Figure 6-4). From these contours, it was seen that growth magnitude increases at greater strains, with decreasing material growth (Figure 6-4a) and increasing thickness growth (Figure 6-4b) as tissue modulus increases. Using the β -parameter to scale the amount of bending stiffness growth assigned towards both modulus and thickness growth allows the model to better represent the understood growth patterns of pediatric bone throughout the aging process.



Figure 6-4: Contour plots representing the proportion of maximum bending stiffness growth $(\Delta E I_{max})$ assigned towards material growth (ΔE) (a) or thickness growth (ΔI) (b) as a function of modulus and strain for bone elements.

6.3. Update Methodology for Fontanelle Tissue

Physiologically, the growth of fontanelles, the fibrous tissue regions located at the junction of three or more cranial bones, is attributed to mechanical loading which can be quantified in terms of mechanical strain similar to bone tissue. Unlike the growth of bone tissue, however, fontanelles have an advanced rate of stiffening, ossifying from their fibrous state to bone tissue between the first few months and first few years of life (Motherway et al. 2009). It has also been found that fontanelles maintain their thicknesses throughout their existence so that their thicknesses at birth are approximately equal to their thicknesses at their age of fusion (Soboleski et al. 1998). Using these observations in addition to the update process developed for cranial bone tissue, the fontanelle tissue growth model was developed.

Like bone tissue, the update methodology for fontanelle tissue growth was based on updating its bending stiffness in response to mechanical strain. However, since fontanelle tissue maintains its thickness throughout its existence, its bending stiffness update was attributed entirely to adjusting its elastic modulus. Additionally, since fully-fibrous fontanelle tissue stiffens more rapidly than bone, its overall magnitude of bending stiffness growth was greater than that of bone tissue. As the fontanelle tissue takes on boney characteristics with increasing modulus, the tissue growth model approaches the same model used for bone. Once the fontanelle tissue modulus reaches that of bone, it was considered fully ossified and its growth methodology was that of bone.

To determine the extent to which these properties were updated, the current elastic modulus of the tissue and the amount of strain present within the tissue were employed. The overall magnitude of fontanelle tissue bending stiffness growth (ΔEI_{font}) depended on both the strain present within the tissue (ε) and the effective maximum growth rate of the fontanelle tissue ($\Delta EI_{max,eff}$). The maximum effective bending stiffness growth rate for fontanelle tissue was related to the proportion of bone character within the tissue, so it depended solely on the modulus (E) of the tissue. Thus, the fontanelle tissue update process consisted of two sequential steps. First, the modulus of the tissue was evaluated to determine its maximum effective update. Second, the strain experienced within the tissue was evaluated to determine the magnitude of bending stiffness growth, which was attributed exclusively to material growth while the fontanelle tissue was not fully ossified. Each step will be described in detail in the following sections. A flow chart outlining the fontanelle tissue update process is shown in Figure 6-5.



Figure 6-5: Schematic of the fontanelle tissue growth process outlining calculation of an adjusted update rate, $\Delta E I_{font}$, based on modulus and strain. Fontanelle tissue with a modulus greater than E_0 are updated identically to bone elements, as shown in Figure 6-1.

6.3.1. Modulus Evaluation to Determine Maximum Fontanelle Tissue Bending Stiffness Growth Magnitude ($\Delta EI_{max,eff}$)

The maximum effective fontanelle tissue stiffening ($\Delta EI_{max,eff}$) depended on the modulus of the tissue. Tissue modulus was assessed using a function consisting of two maximum bending stiffness update proportions, one corresponding to fully unfused fontanelle tissue ($\Delta EI_{max,font}$) and the other corresponding to bone tissue ($\Delta EI_{max,bone}$). $\Delta EI_{max,font}$ corresponds to the maximum possible update magnitude of the fontanelle tissue when it was in its completely unfused state, which occurs when its modulus is equivalent to its initial value (E_{font}). $\Delta EI_{max,bone}$ corresponds to the maximum possible update magnitude of the fontanelle tissue when it is in its completely fused state, which occurs when its modulus is equivalent to or above that of the initial bone tissue modulus (E_0). Fontanelle tissue moduli falling between the initial fontanelle and bone moduli will be assigned a maximum effective bending stiffness update proportional to the difference between $\Delta EI_{max,font}$ and $\Delta EI_{max,bone}$, reflecting an increasingly bone-like tissue with increasing elastic modulus. This is described in Table 6-3 and shown graphically in Figure 6-6.

Table 6-3: The maximum fontanelle tissue bending stiffness growth proportion, $\Delta EI_{max,eff}$, depends on the tissue modulus in relation to the initial fontanelle modulus, E_{font} , and the initial bone modulus, E_0 .

Ε	$\Delta EI_{max,eff}$
$E \leq E_{font}$	$\Delta E I_{max,font}$
$E_{font} \leq E \leq E_0$	$\left[\frac{\Delta E I_{max,bone} - \Delta E I_{max,font}}{E_0 - E_s} (E - E_s)\right] + \Delta E I_{max,font}$
$E \ge E_0$	$\Delta E I_{max,bone}$



Figure 6-6: (a) Representation of the maximum effective fontanelle tissue update proportion, $\Delta EI_{max,eff}$, which is scaled linearly between, $\Delta EI_{max,font}$ and , $\Delta EI_{max,bone}$ based on modulus.

The maximum bending stiffness update for fontanelle tissue was determined using physiological data for consisting of the elastic modulus of fontanelle tissue, the elastic modulus of bone tissue, and the approximate duration for fusion to occur. This approximated the expected proportion of fontanelle tissue stiffening that would occur for a single growth step between the unfused and fused states assuming a constant linear increase in stiffness growth throughout that age span. A detailed calculation of this parameter is provided in Appendix B. The maximum bending stiffness update for bone tissue is described in Section 6.2.1, with a detailed calculation also provided in Appendix B. Once the fontanelle element reaches the same elastic modulus as the initial bone modulus, its update process was treated identically to that of bone tissue, employing both $\Delta EI_{max,bone}$ and β , as described in Section 6.2.

6.3.2. Strain Evaluation to Determine Fontanelle Tissue Growth Proportion ($\Delta E I_{font}$)

The fontanelle tissue bending stiffness growth proportion ($\Delta E I_{font}$) was determined identically to bone tissue, employing strain thresholds ε_{growth} and ε_{max} to assign a proportion of the maximum tissue update rate towards growth, as described in Section 6.2.1. For fontanelle tissue, this growth was assigned as a proportion of the maximum effective fontanelle tissue update rate, $\Delta EI_{max,eff}$ to increase material stiffness of the tissue, ΔE_{font} , while the fontanelle tissue modulus was below that of the initial bone tissue modulus in the model. Once the fontanelle tissue modulus surpassed the initial bone modulus, the update methodology for bone was used to update both the material stiffness (ΔE_{font}) and thickness (ΔI_{font}), as described in Section 6.2.

6.3.3. Applying Material Growth (ΔE_{font}) and Thickness Growth (ΔI_{font}) to Fontanelle Tissue

Once the specific material and thickness update parameters for fontanelle tissue were determined, they were assigned to update the tissue modulus, E, and thickness, t, as proportions of their current values (Equations 6-6 - 6-8). Material growth was applied directly, while thickness growth was applied as a cubic factor of the thickness update, as described in Appendix C, once the tissue modulus surpassed that of the initial bone modulus.

$$E_f = E_i * \Delta E_{font} \tag{6-6}$$

If
$$E_i < E_{bone} \to t_f = t_i$$
 (6-7)

If
$$E_i \ge E_{bone} \to t_f = t_i \sqrt[3]{\Delta I_{font}}$$
 (6-8)

Since the overall bending stiffness update proportion, ΔEI_{font} , was a function of strain, and the specific material (ΔE_{font}) and thickness (ΔI_{font}) update components were functions of both modulus and strain, response contours were created to represent fontanelle tissue growth (Figure 6-7). From these contours, it was seen that the update rate of fontanelle tissue exceeded that of bone while the tissue was considered unfused, that growth magnitude increased at greater strains, and that material growth decreases as tissue modulus increases (Figure 6-7a), while thickness growth increases as tissue modulus exceeds beyond that of the initial bone modulus, corresponding to ossification (Figure 6-7b). These implementations allow fontanelle tissues in the model to act similarly to their understood physiological behavior with aging.



Figure 6-7: Contour plots representing the proportion of overall fontanelle bending stiffness growth (ΔE_{font}) assigned towards material growth (ΔE_{font}) (a) or structural growth (ΔI_{font}) (b) as a function of modulus and strain for bone elements and node pairs.

6.4. Update Methodology for Suture Tissue

During the cranial growth process, bone growth occurs at the interface of bone tissue and suture tissue, which is the fibrous region connecting two skull bones, due to the presence of mechanical stimuli (Katsianou et al. 2016). These mechanical stimuli impose strains upon the suture tissue and cause it to stretch. When this occurs, the bone fronts on either side of the suture move away from one another, providing a location for new bone growth and simultaneously triggering osteogenic cells to undergo ossification in those locations (Katsianou et al. 2016). In a simplified sense, the presence of strain on suture tissue results in the *maintenance* of suture, and the absence of strain results in the *closure* of suture. For this reason, certain sutures in the skull remain present until adulthood, with some never obtaining full fusion (Chiba et al. 2013). The suture growth process is fundamentally different than the growth of bone and fontanelle tissue, which occurs through increases in modulus and thickness in the presence of prolonged mechanical loading. Therefore, using the observation that growth occurs at the bone-suture interface, the analytical suture tissue growth model was developed.

The analytical model for suture tissue growth was based on updating its effective modulus by adjusting the proportion of the tissue that was comprised of suture material and the proportion comprised of bone. The extent to which the proportion of suture was reduced within the tissue (Δw) depends exclusively on the strain that the tissue was experiencing (ε). Therefore, the suture tissue update process consists of a single step involving evaluation of strain to determine the alteration in the suture and bone material composition of the tissue. From the resulting composition, a new effective modulus for the tissue (E_{eff}) was determined. The strain evaluation and effective modulus calculation process for suture tissue will be described in the following sections. A flow chart outlining the suture tissue update process is shown in Figure 6-8.



Figure 6-8: Schematic of the suture tissue growth process showing determination of suture and bone proportions and the corresponding calculation of the effective suture tissue modulus.

6.4.1. Strain Evaluation to Determine Change in Suture Tissue Composition (Δw)

The change in suture material composition within the suture tissue depends solely on the strain within the tissue. The applied strain was assessed employing a function that consists of a single strain threshold (ε_{suture}). This threshold corresponds to the strain for which the suture composition within the material will be maintained at its current amount. Since the presence of

strain results in the maintenance of suture tissue, strains exceeding this magnitude will not result in an update of the suture material. Conversely, since absence of strain results in the closure of sutures and the corresponding reduction in the composition of suture material, the complete absence of strain within the tissue will result in a reduction of suture material in the tissue by a maximum amount, Δw_{max} . Tissue strains falling between 0 and ε_{suture} will be assigned a suture material reduction update proportional to the maximum reduction amount, as described in Table 6-4 and shown graphically in Figure 6-9.

Table 6-4: The suture closure proportion, Δw , depends on the strain within the tissue in relation to the predefined strain threshold, ε_{suture} .

<u>Suture Element Strain (ε)</u>	Suture Width Decrease Proportion (Δw)
$\varepsilon < \varepsilon_s$	Δw_{max}
$arepsilon_s \leq arepsilon < arepsilon_0$	$\left(\frac{\Delta w_{max}}{\varepsilon_{suture}} ight)*(\varepsilon_{suture}-\varepsilon)$
$arepsilon \geq arepsilon_0$	0



Figure 6-9: Representation of the suture closure proportion, Δw , which is scaled linearly between, 0 and Δw_{max} based on the strain within the tissue.

The maximum suture material reduction amount, Δw_{max} , was determined using physiological data for the average suture widths throughout the pediatric skull at the initial and final ages of the growth model (6-months and 2-years) as well as the number of steps in the simulated growth process (1.5 years, or 78 1-week steps). This was a negative value corresponding to the expected proportion of suture closure that would occur for a single growth step between 6months and 2-years of age assuming a constant linear closure in suture during that age span. A detailed calculation of this parameter is provided in Appendix B.

6.4.2. Determining the Bone and Suture Components and Effective Modulus of Suture Tissue

In the model, effective modulus of suture tissue was determined by assigning a proportion of the overall element (w_{total}) to suture material (w_{suture}) and a proportion to bone material (w_{bone}). In its initial state, the entirety of the tissue was considered to be comprised of suture material. Therefore, the initial suture tissue modulus was equivalent to the predefined suture modulus (E_{suture}). Since the proportion of the tissue comprised of suture material decreases through the growth process, the effective modulus (E_{eff}) approaches that of bone (E_{bone}) as shown in Equation 6-9. It is worth noting that w_{total} corresponds to the element width at the conclusion of a growth step because it is assumed that added material from the growth process is attributed to bone, thus increasing the bone composition and effective modulus of the tissue.

$$E_{eff} = \left(\left(\frac{w_{suture}}{w_{total}} \right) E_{suture} \right) + \left(\left(\frac{w_{bone}}{w_{total}} \right) E_0 \right)$$
(6-9)

The modulus of the suture component of the tissue, E_{suture} , was assumed to be the initial suture modulus for each growth step, since prior studies have found that suture does not appreciably stiffen with aging (Coats et al. 2006); additionally, the modulus of the bone portion of the element, E_0 , was assumed to be the initial modulus for bone tissue. Like fontanelle tissue,

prior studies have indicated that suture tissue maintains its thickness during aging (Soboleski et al. 1998). Therefore, no thickness growth was applied to suture elements in the model.

6.4.3. Applying Material Growth to Suture Tissue

Since change in suture tissue effective modulus, ΔE_{eff} , depended on both the proportion of the tissue comprised of suture (w_{suture}/w_{total}) and the strain within the tissue, it was represented using a contour plot (Figure 6-10). From this plot, it was seen that at lower strains, there were greater increases in modulus, indicating a greater magnitude of suture closure in the absence of strain. Additionally, for identical strains, modulus change was greater when the tissue was comprised of a greater proportion of suture material, indicating greater amounts of suture closure with increased suture composition within the tissue. Adjusting the composition of suture tissues in the absence of sufficient mechanical strain enables enhanced representation of their observed physiological growth patterns with aging in the model.



Figure 6-10: Contour plot representing the change in effective suture element modulus (ΔE_{eff}), which depends on the proportion of element width corresponding to suture and the strain within the element.

6.5. Tissue Remodeling Summary

Structural remodeling methods were developed for tissues corresponding to the anatomical features of the growing pediatric skull, specifically bones, fontanelles, and sutures. For each tissue type, growth was assigned in response to maximum principal strain. Based on the findings of prior physiological studies of the pediatric skull, bone tissue was grown by updating modulus and thickness, fontanelle tissue was grown by updating modulus at a more rapid rate based on its modulus, and suture tissue was grown by altering its effective modulus in response to its composition of suture material.

To develop a computational model for pediatric skull growth, the previously developed structural remodeling methods must be implemented into a FE model of the pediatric skull. To translate tissue growth to element-specific growth within a pediatric skull model, the strain, modulus, and thickness of each element in the model must be evaluated and updated individually according to its tissue-specific identity. In doing this, appropriate updates can be applied in accordance with anatomy-specific growth trends occurring through the aging process. If the skull can be expanded corresponding to these aging trends, the underlying remodeling methods can be employed to understand the patterns of pediatric skull shape, material growth, and thickness growth with age.

CHAPTER 7: DEVELOPMENT OF A SIMULATION METHOD TO MODEL PEDIATRIC SKULL GROWTH

Physiologically, it is known that growth of the pediatric skull occurs in response to expansion of the growing brain. This expansion process initiates mechanical forces on the skull which lead to the onset of growth (Katsianou et al. 2016). In general, growth of the pediatric skull occurs by altering material stiffness, localized thickness, and overall shape.

In this chapter, a method to model growth of the pediatric skull is described. Following a generalized structure of a biological computational growth model, an initial FE model of the pediatric skull will be grown from an initial age state of 6 months to a final age state of 2 years. The structural remodeling process developed for bone, fontanelle, and suture tissue in Chapter 6 will be implemented for elements in the model corresponding to these anatomical features. By doing this, the progression of material stiffness change, thickness change, and growth shape of the skull can be updated in response to the forces imparted by the expanding brain using an iterative approach. This will facilitate understanding of predicted cranial growth trends with age.

7.1. General Structure of a Biological Computational Growth Model

7.1.1. General Growth Model Applied to Pediatric Skull Growth

The overall objective of a biological computational growth model is to predict developmental changes that occur in response to a stimulus (Weinans et al. 1992). Stimuli, typically applied as mechanical forces, induce localized stresses and strains within the model. Since it is well understood that biological systems adapt themselves to the loading conditions imposed upon them by attaining a new equilibrium state, these stresses and strains must be mitigated (Weinans et al. 1992). To do this, the system must alter its configuration, which can occur by adjusting its shape or its internal structure (Weinans et al. 1992). This occurs repeatedly over time in response to development to simulate the growth process.

To predict the changes that occur in response to the imposition of mechanical stimuli for the cranial development process, this computational growth model was organized with an iterative structure consisting of simulation and analysis components. Each iteration corresponded to a discrete time interval representing a period of aging. For each iteration, the model was analyzed by assessing the strain within each model element. The model was then updated based on that strain in accordance with its specific anatomical component as outlined in Chapter 6. By aging, analyzing, and updating the model for each time interval, the cranial growth process was simulated.

7.1.2. Growth Model Framework

The framework of a computational growth model enables it to capture the developmental processes that occur in response to mechanical stimuli resulting from forces associated with biological growth. This general framework, shown graphically in Figure 7-1, was applied specifically to the pediatric skull model developed in this thesis. The components of this framework are outlined in this section.



Figure 7-1: The general framework for a biological computational growth model.

Initial Model Configuration

The initial iteration of a growth model was seeded with two primary components: a baseline finite element model that represents a known initial configuration and predefined input parameters that inform the model on how to update during the growth process. Starting from the initial baseline model for the first aging step, initial values related to the properties of the model were stored and a prescribed growth step was applied by running an implicit FE simulation.

Post-Simulation Analysis and Model Update

Due to the implicit simulation which grows the model from one age state to the next, the model will have a distribution of mechanical forces imposed upon it. Based on this mechanical loading distribution and the specific tissue growth model that is employed, an update was individually assigned to each element in the model. In a general sense, the element can be grown, resorbed, or maintained in response to the mechanical force for the subsequent iteration. This can be done by updating information such as its nodal coordinates or material properties to alter its structural characteristics. After completing this update process, values related to the current configuration of the model were stored and a new version of the model was generated to reflect the specific modifications.

Additional Iteration Cycles

Once the model coordinates and element properties were updated, another iteration was run using the updated model following the same process as before: running an implicit simulation that grows the model through a prescribed aging process, analyzing the distribution of a mechanical property throughout the model, and updating the model based on that mechanical property distribution. Iteration cycles were repeated until the desired final age of the model was reached. After reaching this final age, the configuration of the resulting model represented the predicted state using the specific combination of parameters selected for the tissue growth model.

7.2. Pediatric Skull Growth Model Elements

In this pediatric skull computational growth model, elements correspond to specific structural component of the developing skull, including bone, fontanelle, and suture. While there are several possible element types that could have been implemented, thick shell elements were Thick shell elements were selected because they exhibit specific chosen for this model. characteristics of solid and shell elements that are both important towards capturing the appropriate bending loading response of cranial bones, fontanelles, and sutures. They consist of 8 nodes, with 4 nodes defining the bottom surface and 4 nodes defining the top surface (Figure 7-2). Additionally, they contain integration points oriented through the thickness of the element similar to shell elements (Figure 7-2). Due to the presence of nodes at each corner of the element, thick shell elements can capture stresses perpendicular to the element surface like solid elements (Bindeman 2017). Additionally, due to the presence of integration points through the thickness of the element, they exhibit a bending behavior like shell elements (Bindeman 2017). By having the combined capacity to respond to stresses perpendicular to their surfaces and to exhibit bending behavior, thick shell elements act similarly to pediatric cranial bone and can therefore exhibit more biofidelic responses under loading conditions imparted through cranial growth.



Figure 7-2: Thick shell elements possess 8 nodes and through-thickness integration points (Adapted from Bindeman 2017).

Since it was assumed that the loading initiated during the growth process does not cause plastic deformation of the skull, and that the magnitude of strain was much smaller than the ultimate tensile strains measured in Chapter 5, elements were considered as an elastic material. Additionally, while it is known that the pediatric skull exhibits directionality in its loading response, the materials in this study were assumed to be isotropic because there is not consensus in literature regarding how property directionality varies throughout the skull. Therefore, elements were modeled using an isotropic linear elastic material suitable for thick shell elements. The properties of the initial model, including moduli, densities, and Poisson's ratios of each element, were established based on the findings of this study as well as values present in literature. These initial input properties are given in Table 7-1 for elements corresponding to bone, fontanelle, and suture components, with fontanelle and suture elements possessing the same initial properties based on the understanding that they have the same soft-tissue material composition (Crandall et al. 2013).

<u>Input Property</u>	<u>Element Type</u>	<u>Input Value</u>	<u>Source</u>
Modulus, E (MPa)	Bone	1500	This Study, Margulies & Thibault (2000), Coats & Margulies (2006)
	Suture	8.325	Coats & Margulies (2006), Li et al. (2017)
Density, ρ (kg/m ³)	Bone	2150	Coats et al. (2007), Loyd (2011)
	Suture	1130	Coats et al. (2007), Li et al. (2017)
Poisson's Ratio, v	Bone	0.22	Motherway et al. (2009), Giordano & Kleiven (2016)
	Suture	0.49	Coats et al. (2007), Li et al. (2017)

Table 7-1: Input properties for bone and suture elements for the initial model configuration.

7.3. Baseline Pediatric Skull FE Model

The baseline pediatric skull model used in this study was developed using geometry from a 6 month-old single-subject male infant cranial finite element model produced by the University 91 of Michigan (Li et al. 2015), and refined for this study to improve mesh resolution and element quality. The model, shown in Figure 7-3, consisted of 5289 thick shell elements and was organized with a single element through the thickness of the skull. The model contained specific parts corresponding to the cranial suture throughout the skull, the left and right frontal bones, the left and right parietal bones, the occipital bone, and a single component representing the base of the skull that comprises the left and right sphenoid and temporal bones and the inferior portion of the occipital bone.



Figure 7-3: The baseline pediatric skull FE model representing the average geometry of a 6month old pediatric individual and containing specific anatomical features.

This geometry was morphed to a set of landmark points generated from a statistical growth model that was continuously scalable with age between this initial age (6 months) and the final age simulated by the growth model (2 years) (Li et al. 2015). In addition to enhancing the physical model geometry, the model files were updated so that all elements were defined as individual parts. This enabled each element to have its own unique material properties so that updates could be applied at a higher resolution within the model to better represent the growth process.

7.4. Iterative Growth Process

The iterative growth portion of the computational growth model was structured as a loop where each growth iteration corresponded to a single cycle of the loop. For the growth process employed in this model, the number of iterations of the loop was equivalent to the number of weeks of simulated growth. In this study, the model was grown from an initial age of 6 months to a final age of 24 months, meaning there were 78 weeks of growth and an associated 78 growth iterations. Iterations consisted of simulation, analysis, and update components. Prior to running the simulation, the specific magnitude to expand the cranial volume of the model was required. Additionally, the moduli and thicknesses of all elements in the model were stored for future update based on the simulation results. A detailed outline of the organizational framework and analysis variable structure implemented for this pediatric skull computational growth model is outlined in Appendix D.

7.5. Assignment of Volume Expansion Scale Factor

The first step in the iterative growth process was the growth simulation. The load increment applied to the skull model was determined by expanding the model intracranial volume by a predefined amount based on the change in pediatric intracranial volume as a function of age. Pediatric intracranial volume (ICV) was determined using a previously developed function based on 157 individual subject CT-scans that was demonstrated to trend similarly with other functions present in literature (Abbott 2000). First, the specific intracranial volumes for the initial and final ages of each growth iteration were determined using this previously developed function, which was shown graphically in Figure 7-4 below for both male and female individuals (the male response was simulated in this study). Then, a change in volume for each iteration was determined by calculating the difference between the projected intracranial volumes for all initial and final
growth iteration states. Each of these volume changes was then incorporated into the simulation using a pressure-volume relationship within the enclosed finite element volume.



Figure 7-4: Intracranial volume versus age curves for 0 to 36 months from Abbott (2000) were used to determine the scale factors needed to grow the skull model by the required volume magnitude for each iteration. Male skull growth was simulated for this model.

This model resulted in the application of a uniform pressure to a control volume through the influx of mass over a specific time interval. The specific control volume of the model was the inner surface of the skull. By rearranging the relationship followed by the model, which determines applied pressure as a function of the desired volume, volume can be determined as a function of the applied pressure through Equation 7-1 below, where V_0 and V_f are the initial and final skull volumes, P_f is the final pressure inside the skull, ρ and K are the density and bulk modulus of the control volume material, respectively, dm/dt is the mass flow rate of the control volume material during the time interval t_i to t_f , and α is a scale factor that can be used to control the magnitude of mass flow for each iteration.

$$V_f = exp\left(-\frac{P_f}{K}\right) \left[\frac{V_0\rho + \int_{t_i}^{t_f} \alpha \frac{dm}{dt} dt}{\rho}\right]$$
(7-1)

After several trials to determine the loading approach needed to minimized volumetric expansion error, the best approach was determined to be a trapezoidal-based mass flow rate which involves holding the rate at 0 initially, conducting a linear ramp to the desired peak mass flow rate, holding at that mass flow rate, and decreasing the mass flow rate linearly back to 0 so that it equals 0 at the termination of the simulation. The α -parameter was implemented as a scale factor for the mass flow rate to control the precise magnitude of volume expansion. This parameter was updated prior to the initiation of each simulation iteration to ensure the proper magnitude of volume expansion was carried out.

7.6. Growth Simulation

After finalizing the model volume expansion characteristics, the growth simulation was run. Typical simulations took between 30 and 35 seconds per iteration to complete. At the conclusion of an iteration of growth, there was a non-uniform strain distribution throughout the model corresponding to equilibrium state resulting from the increase in cranial volume, as shown in Figure 7-5. The growth shape of the skull differed as a result of the applied expansion process and the moduli and thicknesses of elements within the model.



Figure 7-5: Skull strain distribution for an intermediate growth iteration. The strain distribution was used to inform updates of element moduli and node pair thickness throughout the model.

7.7. Simulation Analysis and Model Update for the Following Iteration

After a simulation was run, the strain states and thicknesses of all elements in the model, and all nodal coordinates within the model were output. Using the strain information along with previously stored element moduli and thicknesses data, tissue growth updates were assigned on an element-by-element basis according to the specific processes outlined in Chapter 6 for bone, fontanelle, and suture elements.

Once updated moduli and thicknesses were determined for each element in the model, a new FE model was generated. To represent the updated growth shape, the new FE model implements the post-simulation nodal coordinates. Additionally, to represent the updated structural features, this updated model incorporated the new moduli and thicknesses for each element. A detailed outline of how the specific updates were applied to generate the new FE model for the subsequent simulation iteration is provided in Appendix E.

Once generated, the newly-produced FE model based on the simulation analysis was used for the subsequent simulation iteration, following the iterative structure outlined above. This iterative growth process continues identically to the process outlined above for each iteration until the final desired growth age of the model was reached.

7.8. Skull Growth Simulation Baseline Results

An initial baseline growth simulation was run to assess the performance of the pediatric skull growth model at capturing cranial growth with age. This growth simulation employed the input parameters shown in Table 7-1 and was run from an initial age state of 6-months to a final age state of 2-years. After running the simulation, the model exhibited variations in shape, modulus, and thickness as a result of to the growth process. Developmental variations within the model arose both as a result of the strain distribution initiated throughout the model due to cranial expansion as well as the anatomy-specific tissue growth methodologies employed for elements within the skull model corresponding to bone, fontanelle, and suture tissues.

Variations throughout the skull resulting from the growth simulation evolved during the course of the simulation, with more drastic magnitudes of growth between earlier age states than later age states due to greater expansion magnitudes and greater corresponding strains for earlier growth iterations. Specifically, this was seen for growth shape, elastic modulus, and thickness variation throughout the skull. Growth shape of the skull model, shown in Figure 7-6, progressed by lengthening in the anterior-posterior and superior-inferior directions as well as by developing a more oval-shaped configuration in the coronal plane. Elastic modulus increased most substantially between the earlier age states and appeared to be the largest at the inferior portion of the parietal bone and along the parietal bone-coronal suture interface, as shown in Figure 7-7. Similarly, the greatest changes in skull thickness occurred at the inferior portion of the parietal bone and along the parietal bone the earliest ages states (Figure 7-8). The increased moduli

and thickness changes in these cranial regions can likely be attributed to greater regional strains arising from the growth process and corresponding increases in growth magnitude.



Figure 7-6: Growth shape in the sagittal (a), coronal (b), and transverse (c) planes for a pediatric skull growth simulation for 6-month, 12-month, 18-month, and 24-month age states indicating changing growth shape with age.



Figure 7-7: Modulus distribution for a pediatric skull growth simulation for 6-month, 12-month, 18-month, and 24-month age states demonstrating greater shape changes between earlier age states.



Figure 7-8: Thickness distribution for a pediatric skull growth simulation for 6-month, 12month, 18-month, and 24-month age states demonstrating greater shape changes between earlier age states.

Additionally, variations among individual bones, fontanelles, and sutures within the model were observed. Starting from the same initial moduli, it was seen that individual cranial bones exhibited different moduli (Figure 7-9a) as well as increasing thicknesses (Figure 7-9b) with age, though these differences were not significant for this baseline case. Individual fontanelles exhibited ossification between 0 and 6 months; additionally, their moduli differed from one another to a greater extent with age (Figure 7-10). Finally, different sutures exhibited different effective widths (Figure 7-11a) and corresponding difference in effective modulus (Figure 7-11b) throughout the growth process. These differences among anatomical components in the model emphasize the impact of regional strains during the growth process on the resulting growth pattern exhibited throughout the model.



Figure 7-9: Bone tissue predicted modulus (a) and thickness (b) change with respect to individual type and age for a baseline simulation.



Figure 7-10: Fontanelle tissue predicted modulus with respect to individual type and age for a baseline simulation.



Figure 7-11: Suture tissue predicted width (a) and effective modulus (b) respect to individual type and age for a baseline simulation.

By predicting the trends in development that occur with increasing age, this model can potentially provide enhanced insight into the pediatric cranial growth process. The developmental trends predicted by this model can be verified through comparisons with experimental and biometric pediatric skull data.

7.9. Skull Growth Simulation Summary

A simulation method to model growth of the pediatric skull was developed. This method applied an iterative approach, where each iteration corresponded to a discrete advancement in age. For each iteration, model growth was simulated by expanding the ICV of a pediatric skull FE model by a prescribed magnitude corresponding to an ICV versus age relationship established in literature. The strain distribution throughout the model resulting from this expansion was then analyzed, element-specific growth was applied according to the remodeling methods developed in Chapter 6 for each specific anatomical feature within the model, and a new model containing the updated growth characteristics was generated for the subsequent iteration.

After developing a growth simulation method for the pediatric skull and implementing element-specific update methodologies based on anatomical features, the model was capable of representing variations in growth shape, material property, and thickness in response to aging. Since the model was limited by the current availability of data regarding the pediatric skull, it was important to assess its sensitivity to a variety of input parameters to understand which were most important to consider for future model versions moving forward.

CHAPTER 8: PARAMETRIC ANALYSIS OF THE PEDIATRIC SKULL COMPUTATIONAL GROWTH MODEL

Parametric analysis of computational models is an important tool by which model outputs can be systematically compared to assess their similarity and accuracy in correspondence with physically observed data. Therefore, this approach was used to evaluate the performance of this pediatric skull computational growth model in its current form. In this chapter, two parametric analysis components will be done for this model; additionally, the model will be applied to assess its ability to capture physiologically-observed growth variations resulting from a pathological condition.

For the first parametric analysis, the ability of the model to predict the physiological growth shape of the pediatric skull was assessed in response to different input parameters. This was done by comparing the final configuration of the growth model to a set of statistical landmark coordinates corresponding to the shape of the pediatric skull (Li et al. 2015). This will allow the general shape of the pediatric skull predicted by the model to be compared to the observed shape that was determined through averaging a collection of pediatric CT scans, providing insight into the accuracy and sensitivity of the pediatric skull growth shape predicted by the model in response to variations in input parameters.

For the second analysis, the sensitivities of model structural outputs will be assessed in response to different input parameters. The specific structural outputs that will be assessed include the final moduli and thicknesses of bone elements in the model, both overall and by specific bone type, and the final effective suture widths of suture elements in the model, both overall and by specific suture type. Due to a lack of consensus across prior experimental studies regarding age-specific data for the pediatric skull, this involves comparing general trends in responses as opposed to numerically evaluating outputs. This will allow both the physiological basis of the update

methodologies employed in the model as well as the growth trends predicted by the model to be evaluated in relation to the structural-level changes in pediatric cranial growth.

The application of this model will involve simulating the pathological condition of craniosynostosis and analyzing model growth. Understanding model behavior in response to this pathological condition will provide insight into the impact of structural property variations and anatomy-specific element update methodologies on the resulting growth pattern predicted by the model. This can be assessed in relation to physical observations to understand the model's predictive capacity in its preliminary form.

Taken together, the analysis components performed in this section enable assessment of the model's ability to predict physiologically-observed developmental trends for the pediatric skull. Understanding model performance in response to a range of various input parameters is useful to assess the predictive capability of the model in its current state and to highlight focus areas for model development moving forward.

8.1. Parametric Analysis Setup and Analysis Approach

8.1.1. Parametric Analysis Structure

To analyze this computational growth model, a full factorial design was employed. This design involves multiple input parameters, with each input parameter containing multiple possible values, known as levels. For each combination of input parameter and level, a single experimental run was performed. This means that the sample size for a full factorial design is the product of the number of levels of each of the parameters. The validation framework implemented for this model consisted of five input parameters, each with three levels. Therefore, to employ a full factorial design, $3^5=243$ simulations were required.

8.1.2. Input Parameters

Due to the lack of definitive age-specific data regarding many aspects of the pediatric skull, its growth and development process was not well characterized. Because of these limitations, this model was constructed using several assumptions to guide the growth process, with specific methodologies developed for bone, fontanelle, and suture tissues, as outlined in Sections 6.2-6.4. Using these assumptions introduces an inherent uncertainty related to the accuracy of the model. Therefore, to assess their impact on the underlying growth pattern of the model, five variable input parameters were studied. Each of these parameters is shown in Table 8-1 below alongside its specific levels, areas of growth that it affects, and specific reference section. Input parameters were linked to the growth model update process by controlling the processes for bending stiffness growth rate and magnitude for bone, fontanelle, and suture elements.

Table 8-1: Input parameters for the growth model validation framework. Each combination of parameters was simulated to employ a full factorial design. Parameters corresponded to the calculated growth rates and magnitudes for bone, fontanelle, and suture elements in the model, as outlined in Chapter 6 and Appendix B.

Input Parameter	Levels (Units)	Growth Areas Impacted
1) ε_{growth}	[1E-4, 5E-4, 1E-3] (strain)	Bone / Fontanelle Growth Rate
2) ε_{max}	[1.5E-3, 3.0E-3, 5.0E-3] (strain)	Bone / Fontanelle Growth Rate
3) E _{24mos}	[2,3,4] (GPa)	Bone Growth Magnitude
4) n _{fusion}	[12, 24, 36] (months)	Fontanelle Growth Magnitude
5) ε_{suture}	[1E-3, 3E-3, 5E-3] (strain)	Suture Width Change Rate

8.1.3. Physiological Basis for Input Parameters

Of the five input parameters implemented for the model, three act to control strain thresholds for growth and two act to control bending stiffness growth magnitudes. For the parameters controlling strain thresholds, growth strain (ε_{growth}) and max strain (ε_{max}) collectively control the thresholds at which bone and fontanelle elements are updated and correspondingly scale the specific magnitude with which these elements are grown. Suture strain (ε_{suture}), on the other hand, controls the strain threshold at which sutures remain patent. While it is known that strain drives the magnitude of growth observed in bone (Weinans et al. 1992; Lee et al. 2019) and that strain at the bone-suture interface causes them to remain patent (Katsianou et al. 2016), there is currently no available data regarding the quantifiable strain values at which bone or fontanelle growth occurs or sutures remain patent. Therefore, the specific levels for each of these parameters were selected empirically, rather than physiologically, to elicit different responses for model growth and to understand how their different magnitudes impact the model growth response.

The other input parameters, 24-month-old modulus (E_{24mos}) and fontanelle fusion age (n_{fusion}), had levels selected based on the range of currently predicted literature values for each, with 24-month old bone moduli ranging being between 2 GPa and 4 GPa and fontanelles fusion ages ranging between 12 and 36 months according to prior studies and predictive models. By varying each of the five input parameters across simulations, an understanding of the importance of each of these processes on the underlying structural and shape-related patterns could be understood.

8.1.4. Parametric Analysis Comparison Metrics

After running the full factorial design for all combinations of input parameters for this model, the results of all simulations will be analyzed for each parametric analysis component.

Physiological Growth Shape

As previously mentioned, the first parametric analysis will evaluate the ability of the model to predict the physiological growth shape of the pediatric skull in comparison to the landmark coordinates obtained from the pediatric skull statistical model developed by Li et al. (2015). The

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model was produced from a collection of 56 head CT scans from children ranging from birth to three years of age and consists of 60 landmark coordinates for locations throughout the outer surface of the skull which were continuously scalable within that age range as a function of skull circumference.

The comparison metric across simulations for this skull shape assessment was the average distance from the predicted statistical model landmark coordinate to the nearest surface of the skull growth model for the final two-year-old simulated age, which was within the predictive range of the model. This comparison will be made for the entire collection of landmark points as well as for collections of landmark points corresponding to specifically defined physiology (suture and bones) of the skull model.

To determine the distances from each landmark point to the skull growth model surface, the skull model was aligned through rigid body rotation so that it was in the proper configuration with respect to the landmark coordinates. Following rigid body rotation, the minimum distance from each landmark point to the skull model surface was found by determining the closest model surface to each of the landmark points.

Model Structural Outputs

As noted earlier, the second parametric analysis was to assess the sensitivity of model structural outputs to each combination of input parameters. The specifically assessed outputs will include modulus and thickness for bone elements and width for suture elements. All outputs will be determined for the final state of each model as an average value both across all elements in the model and for specifically defined bones and sutures defined within the model.

8.1.5. Statistical Analysis Methods

Generalized Linear Model Analysis

After determining the average parameters for each validation component for all simulations of the full factorial design, the results will be analyzed using a generalized linear model (GLM). These models consist of a response variable that was modelled by a linear function of explanatory variables, taking the form seen in Equation 8-1 below, where \hat{y} is the output value, β_0 is the intercept, β_i -values are the parameter estimations for each of *i* input parameters, and x_i -values are the specific input values for each corresponding input parameter, *i*. This model acts identically to a multi-way analysis of variance (ANOVA) approach, where the significance of input parameters within the model were assessed in relation to their effect on the specific output parameter (Dobson & Barnett 2008). However, unlike ANOVA, the GLM approach can account for continuous input parameters, such as those used for this model, and can also provide specific parameter estimates for the model to predict outputs (Dobson & Barnett 2008). Therefore, since it can effectively assess the relative significance of each growth model input parameter as it relates to the corresponding model shape or structural output, and since it can accommodate a continuous range of inputs, these validation simulations will be evaluated using the GLM approach.

$$\hat{y} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_i x_i \dots$$
(8-1)

In addition to determining the significance of individual input parameters on the response, the GLM analysis approach, like ANOVA, can also account for interactions between input parameters. Interactions exist when the predicted effect of one input parameter on the response specifically depends on the value of the other input parameter with which it interacts. This enables the model to explain the variability present within the response to a greater extent and can thus make the model more useful (NIST). This GLM representation with interaction is shown in Equation 8-2, where additional β_{ij} -terms are present for multiplied combinations of input parameters *i* and *j* used to predict the specific output response. Applying the GLM analysis approach to this full factorial design with incorporation of interaction terms will provide a clearer understanding of the underlying effects of each input parameter, and how they vary alongside one another, on the specific component of the model response.

$$\hat{y} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \cdots$$
 (8-2)

After producing a GLM representation for each model output parameter, there were often terms that were not significant predictors for the output. To create a model that provides both maximum simplicity and explanatory power, a stepwise approach was applied. This approach began with an initial statistical model and iteratively added to or eliminated terms from the model by assessing how the addition or removal of the term affected the resulting p-value for the model *F*-statistic in comparison to that of the previous model. By applying this approach, an enhanced linear model that maximized explanatory capability was created for the output.

One-Way Analysis of Variance

Since the landmark coordinates and skull model surface could vary differently for different locations throughout the skull, one-way ANOVA will be applied for individual simulations to understand how locational accuracy varies throughout the model. One-way ANOVA evaluates the hypothesis that samples from multiple datasets belong to populations with the same mean (Dobson & Barnett 2008). Performing these tests will assess which skull regions grow with the greatest resemblance to the landmark coordinates and will also provide insight into location-based growth trends in response to the different input parameter combinations. Additionally, if ANOVA tests indicate significance, Tukey post-hoc comparison tests can be used to determine significant differences in growth patterns between the specific pairs of locations being compared.

Since literature has suggested differences in bone modulus by specific bone type (Crandall et al. 2013), in addition to applying GLM analysis to each validation approach across the totality

of simulations, one-way ANOVA will also be applied for individual simulations to assess differences in predicted bone moduli, bone thicknesses, and suture widths for each bone or suture defined in the model. This will allow for comparison of the modulus growth trends, bone thicknesses, and suture widths for the different input parameter combinations. If ANOVA indicates significance, Tukey post-hoc comparison tests will be used to determine differences in model structural features between the specific bones or sutures being compared.

Applying GLM analysis to parameter-specific geometric shape and structural outputs will allow for assessment of the significance of each input parameter towards the underlying model response. Additionally, performing one-way ANOVA tests will enable understanding of regional differences in output values predicted by the model. These analysis approaches will be useful for future model development moving forward.

8.2. Parametric Analysis Results and Discussion

After running simulations corresponding to each combination of input parameters within the full factorial design framework, the results of the model validation were analyzed to assess the significance of each input parameter towards predicting growth response and to determine the growth variations that occurred throughout the model. This was done for both physiological growth shape and structural output, as outlined in the previous section.

8.3. Physiological Growth Shape

The general growth pattern predicted by this pediatric skull growth model, shown for an example simulation in Figure 8-1, occurred consistently across all simulated input parameter combinations. Throughout the growth process, the model tended to exhibit vertical growth of the frontal bone, seen in the forehead region, as well as horizontal elongation of the superior region of the skull (Figure 8-1a to 8-1b). Additionally, the skull developed a more elongated and oval-like

vertical shape and a more flattened apex region (Figure 8-1c to 8-1d). Huelke (1998) and Silau et al. (1995) noted that the infant skull is initially very rounded before transitioning to a more ovalshaped appearance, both in the coronal and sagittal planes. Since the general shape progressions seen in this model were consistent with the general developmental trends noted in prior studies, this model likely provides a good representation of the general growth shape of the developing pediatric skull.



Figure 8-1: Pediatric skull FE model general predicted growth pattern, showing progression from the initial to final states in the sagittal plane (a to b) and the coronal plane (c to d).

8.3.1. Comparison Across All Simulations

To quantitatively assess the final physiological growth shape of the model in response to each input parameter, the collection of statistical landmark coordinates obtained from Li et al. (2015) were compared to the corresponding nearest points on the skull model surface. Applying a GLM to this assessment, the significance of each input parameter and its associated interaction with each other input parameter was determined. The results of this analysis are shown in Table 8-2 for different collections of landmark points corresponding to different locations on the skull surface. Terms included in the GLM are seen in the table, with asterisks indicating significance.

 Table 8-2: Landmark offset GLM parameters (by row) including input parameter main effects and second-order interaction terms for groups of landmark coordinates (by column).

 All Landmarks
 Sutures
 Frontal Bone
 Parietal Bone
 Occipital Bone

	All Landmarks	Sutures	Frontal Bone	Parietal Bone	Occipital Bone
Intercept	3.09E+00**	2.93E+00**	1.87E+00**	2.93E+00**	4.51E+00**
ϵ_{growth}	-4.54E+00	2.12E+01	1.04E+01	-	-
ε_{max}	9.09E+00*	5.82E+00**	4.57E+01**	-1.29E+01*	-2.32E+01*
E _{24mos}	-9.68E-05**	-1.02E-04**	-1.18E-04**	-5.01E-05**	-1.59E-04**
$n_{fusion,font}$	-	-	5.00E-03**	6.62E-04	-6.59E-03**
<i>E</i> suture	1.49E+01**	9.99E+00**	3.17E+01**	2.42E+01**	2.34E+01**
$\boldsymbol{\varepsilon}_{grow}$: $\boldsymbol{\varepsilon}_{max}$	-1.49E+04**	-2.39E+04**	-1.10E+04*	-	-
ε_{grow} : E_{24mo}	2.35E-02**	2.89E-02**	2.53E-02**	-	-
$arepsilon_{grow}$: n_{fus}	-	-	-	-	-
ε_{grow} : ε_{suture}	-	-	-	-	-
ε_{max} : E_{24mo}	1.28E-02**	1.43E-02**	8.66E-03**	1.06E-02**	2.35E-02**
ϵ_{max} : n_{fus}	-	-	-5.48E-01**	8.12E-01**	1.11E+00**
ε _{max} : ε _{suture}	-	-	-	-	-
E_{24mo} : n_{fus}	-	-	9.78E-07**	-5.95E-07**	
E_{24mo} : ε_{suture}	-	-	-	-	-
n_{fus} : $arepsilon_{suture}$	-	-	-8.26E-01**	-	-

(Units: mm) (* indicates p<0.05 and ** indicates p<0.001)

As seen in Table 8-2, across all groupings of landmark points, ε_{growth} was not a significant contributor towards landmark offset in any case, fontanelle closure age was a significant contributor for groupings involving individual bone landmarks, and other individual input parameters were significant for all groupings. Additionally, the interaction of ε_{growth} with ε_{max} and with E_{24mos} as well as the interaction of ε_{max} with E_{24mos} were generally significant across all groupings. This was seen through the interaction plot for all landmark points, in Figure 8-2b, where offsets vary differently depending on the level of E_{24mos} for both ε_{growth} and ε_{max} , seen with the presence of non-parallel lines. Finally, though the mean landmark offset appears to be fairly consistent across all combinations of input parameters, ranging from ~2.92mm to ~3.08mm average offset for each simulation, when observing the main effects plots in Figure 8-2a for the full set of landmark points, the smallest offsets appears to occur when ε_{max} , or the strain threshold with which growth occurs by the maximum amount, is smallest, E_{24mos} , the predicted final bone modulus, is largest, and ε_{suture} , the strain threshold at which sutures remain in the same state of patency, is minimized. This combination of input parameter magnitudes corresponds to increased bone growth and decreased suture closure in terms of the growth process employed by this model.



Figure 8-2: Main effects plot (a) and interaction plot (b) of each input parameter on mean landmark point offset from the final predicted skull model surface determined across all landmark points in the model.

8.3.2. Comparison Within Each Simulation

The one-way ANOVA test assessing the difference in landmark offset by bone type indicated significant differences for each simulation (Table 8-3). Investigating the pairwise comparisons of landmark offset by specific bone in the skull model revealed that the offsets between frontal and occipital bone, corresponding to the anterior and posterior portions of the skull, significantly differed for each simulation, with the frontal bone landmarks having significantly smaller offsets than those of occipital bone (Table 8-3). Neither of these regions significantly differed from parietal bone, which corresponded to the lateral portion of the skull (Table 8-3).

Table 8-3: One-way ANOVA results and corresponding pairwise comparisons for mean landmark offset by bone type within each individual growth simulation.

Number of	Significant	Pairwise Significance		
Simulations	ANOVA Tests	Comparison	Frequency	
	243	Frontal/Parietal	0	
243		Frontal/Occipital	243	
		Parietal/Occipital	0	

8.3.3. Implications of Findings for Growth Shape

When collectively viewing the effect of input parameters on the resulting offset of the skull model from the predicted landmark coordinates (Figure 8-2), even though the mean offset is fairly consistent at around ~3mm for each combination of growth parameters, it appears that the model more closely resembles the landmark point distribution when the maximum growth strain threshold, ε_{max} , is minimized, the predicted bone modulus at the 24-month old final model age, E_{24mos} , is maximized, and the suture patency strain, ε_{suture} , is minimized, the combination of which corresponding to increased bone growth and decreased suture closure. In addition, each of these parameters was significant towards predicting surface offset for all subsets of landmark points concentrated spatially throughout the skull. Therefore, these three input parameters are potentially the most important towards directing the growth shape of the model in its current form, with increased bone growth and decreased suture closure increasing resemblance between the model and the landmark point distribution.

When understanding the within-simulation results from Table 8-3, the decreased resemblance of the model to the landmark points at the posterior of the skull in comparison to the frontal skull region could be due to inaccuracies of the model at this location which, through repeated growth iterations, may be further compounded so that the offset is increased by the conclusion of the growth simulation. A potential improvement in the initial model configuration could aid in the spatial distribution accuracy of the final model in relation to the landmark coordinates.

Other possible explanations for this increased posterior offset, in addition to all observed offsets between the skull surface and the statistical landmark coordinates, could result from the implemented model growth process and the growth magnitude used.

The growth process implemented in this model was a uniform volumetric expansion, where the interior of the skull was expanded with a uniform outward pressure to reach a desired final volume. Even though it is known that the brain expands in different regional locations at different times during aging, the uniform pressure expansion process was followed because there is currently no information regarding the region-based expansion patterns of the growing brain as there is for widely-studied laboratory animals such as mice (Lee et al. 2019). Information regarding the pressures exerted within the specific regions of the growing brain as a function of age would likely aid in the accuracy of the growth patterns predicted by the model.

Additionally, though the amount of volume expansion was based on a predictive model of intracranial volume (ICV) developed from a pediatric CT database (Abbott et al. 2000), this ICV

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relationship was developed from a different collection of CT scans than the collection of scans used to develop the landmark statistical model points. Due to the large degree of inherent biological variability within the pediatric population and the different collections of CT scans used to inform volume expansion magnitude and statistical landmark point locations, it was highly unlikely that the ICVs and corresponding iteration expansion magnitudes measured by Abbott et al. and the ICVs of subjects used to develop the landmark coordinate sets correspond with one another. Therefore, while based on subjects of the same age, the volume expansion magnitudes for this model were likely not the same as those of subjects used to develop landmark points, likely contributing to observed differences between the model and landmark points.

Overall, though the pediatric skull model predicted the landmark coordinates corresponding to the final age of the model fairly well, there were clear discrepancies between the two. Increased understanding of the influence of strain magnitude contributing to skull growth, the bone modulus for older pediatric individuals, and strain thresholds at which suture remains patent in the skull, all significant input parameters in this model, could potentially improve the accuracy of this growth model. Moving forward, having access to regional-level skull ICV expansion pressure data in addition to landmark points from the same group of pediatric subjects as that used to develop the implemented ICV versus age relationship would likely enhance the ability of the model to predict the growth patterns of the skull moving forward.

8.4. Bone Modulus

The initial state of this pediatric skull growth model assumed an equivalent elastic modulus for all bones within the skull. The value of this modulus, 1.5GPa, was based on the findings of this thesis as well as from previous studies testing parietal bone under bending conditions. After applying the simulated growth process to this model, the modulus varied throughout the skull due to differences in the strain distribution present in different regions of the skull, with different sets of input parameters leading to different resulting modulus distributions. An example simulation demonstrating the variation in elastic modulus distribution is shown in Figure 8-3.



Figure 8-3: Final elastic modulus distribution throughout the skull for a growth simulation demonstrating regional differences.

The variation in modulus found using this computational growth model agrees with the findings of prior studies which have identified differences in the elastic moduli between cranial bones. Specifically, though they did not perform extensive testing, these studies found that parietal cranial bone was generally stiffer than occipital bone and that frontal bone was generally stiffer than parietal bone (Coats & Margulies 2006; Wang et al. 2014). The large degree of variability and limited number of samples across studies only allows for understanding of general trends in modulus as opposed to specific numeric values with aging.

8.4.1. Comparison Across All Simulations

To understand the differences in elastic modulus distribution within the skull in response to the combination of input parameters, a GLM was applied to the mean elastic modulus of the skull model in its final configuration. The results of this analysis are shown in Table 8-4 for all bones as well as for each individual skull bone in the model.

O nus: MFa) (* all lerms appearing in the model possessed a significance of $p < 0.001$					
	All Bones*	Frontal Bone*	Parietal Bone*	Occipital Bone*	
Intercept	2.98E+03	2.91E+03	3.08E+03	2.78E+03	
ϵ_{growth}	-7.31E+05	-7.96E+05	-6.57E+05	-8.41E+05	
ε _{max}	-2.36E+05	-2.32E+05	-2.44E+05	-2.21E+05	
E_{24mos}	3.60E-01	3.75E-01	3.47E-01	3.77E-01	
n _{fusion,font}	-2.82E+00	-3.36E+00	-2.63E+00	-2.63E+00	
ε_{suture}	-	-	-	-	
$\boldsymbol{\varepsilon}_{grow}$: $\boldsymbol{\varepsilon}_{max}$	9.27E+07	1.15E+08	6.49E+07	1.37E+08	
ε_{grow} : E_{24mo}	-1.20E+02	-1.34E+02	-1.04E+02	-1.43E+02	
$arepsilon_{grow}$: n_{fus}	-	-	-	-	
Egrow: Esuture	-	-	-	-	
ε_{max} : E_{24mo}	-3.29E+01	-3.73E+01	-2.83E+01	-3.97E+01	
ε_{max} : n_{fus}	-	-	-	-	
$\boldsymbol{\varepsilon}_{max}$: $\boldsymbol{\varepsilon}_{suture}$	-	-	-	-	
E_{24mo} : n_{fus}	-	-	-	-	
E_{24mo} : ε_{suture}	-	-	-	-	
n_{fus} : ε_{suture}	-	-	-	-	

Table 8-4: Bone modulus GLM parameters (by row) including input parameter main effects and second-order interaction terms for all bones (Column 1) and individual bones (Columns 2-4) (Units: MPa) (* all terms appearing in the model possessed a significance of p<0.001).

(Units: MPa) (* all terms appearing in the model possessed a significance of p<0.001)

Shown in Table 8-4, for all bones as well as each individual bone in the model, all individual input parameters aside from ε_{suture} , the strain threshold driving suture patency, were significant contributors towards varying the bone elastic modulus predicted by the model. Additionally, the interaction of ε_{growth} , the strain level corresponding to the onset of growth, and ε_{max} , the strain level corresponding to the maximum amount of growth, both with each other and with E_{24mos} , the final modulus informing the maximum magnitude of growth, were influential in driving modulus variation within the model. This was seen through the interaction plot for mean final bone modulus in Figure 8-4b, where the final bone modulus varies differently depending on

the levels growth and maximum strain as well as end modulus. This was seen with the presence of non-parallel lines for the combination of each of these inputs.

Viewing this interaction plot alongside the main effects plot for mean final bone modulus, seen in Figure 8-4a, the largest final modulus appears to occur when ε_{growth} and ε_{max} are minimized and E_{24mos} is maximized. Conversely, the smallest final modulus appears to occur in the opposite case, when ε_{growth} and ε_{max} are maximized and E_{24mos} is minimized. This makes sense in terms of the growth process of this model because smaller strain thresholds correspond to an increased prevalence of growth and a larger final modulus corresponds to a greater magnitude of growth (Section 6.2). Additionally, $n_{fusion,font}$, which impacts the rate of fusion of fontanelle elements, was found to be significant towards bone modulus potentially due to the influence of fontanelle elements on the strain and corresponding update magnitude of neighboring bone elements to some extent, though the other significant input parameters appeared to have a much larger influence on bone modulus for the model.



Figure 8-4: Main effects plot (a) and interaction plot (b) of each input parameter on mean bone modulus across all bone elements in the final skull model.

8.4.2. Comparison Within Each Simulation

The one-way ANOVA test used to investigate the difference in bone modulus by bone type for each individual simulation suggested significant differences between moduli for each simulation (Table 8-5). Using Tukey post-hoc tests to investigate pairwise comparisons of bone 121 modulus for each bone type revealed that each pairwise set of skull bones in the model (frontal, parietal, and occipital) significantly differed from one another for each growth simulation (Table 8-5). Within each simulation, parietal modulus was consistently stiffest, followed by frontal modulus, which was the second stiffest, and occipital modulus, which was the least stiff.

Table 8-5: One-way ANOVA results and corresponding pairwise comparisons for mean final bone modulus by bone type within each individual growth simulation.

Number of	Significant	Pairwise Significance	
Simulations	ANOVA Tests	Comparison	Frequency
		Frontal/Parietal	243
243	243	Frontal/Occipital	243
		Parietal/Occipital	243

8.4.3. Implications of Findings for Bone Modulus

When collectively viewing the effect of input parameters on the resulting final bone modulus predicted by the model, it appears that the stiffest average model bone elements result when the strain thresholds initiating growth are minimized and the final predicted modulus is maximized. Conversely, the least stiff average model bone elements result when the strain thresholds and final predicted modulus are maximized and minimized, respectively. Since each of these parameters, as well as the interaction between each of them, was most influential towards driving the final modulus of the skull, and since each was significant in the GLM, they are potentially the important towards directing the elastic modulus predicted by this growth model.

Differences between average predicted moduli were identified for parietal, frontal, and occipital bones using this growth model, which was also documented in previous experimental studies. Specifically, when viewing bones as a whole, parietal bone was found to be stiffer than frontal and occipital bone.

While it could be concluded that these findings were in agreement with Coats & Margulies (2006) for parietal and occipital bones and at odds with Wang et al. (2014) for frontal and parietal

bones, it is known that there is variation in modulus throughout individual skull bones, and that each of these studies tested a limited number of samples from specific locations of each bone. Interestingly, when viewing the sample locations for these studies superimposed on an average modulus distribution for this growth model, the measured trend does appear to hold, with the frontal sample region having a greater modulus than the parietal sample region for Wang et al. (2014) and the parietal sample region having a greater modulus than the occipital sample region for Coats & Margulies (2006) (Figure 8-5). This was likely attributed to the strain distribution initiated during skull growth, indicating that the model likely responds in a realistic manner.



Figure 8-5: Localized predicted skull bone modulus for locations outlined in black boxes generally agrees with that found in prior studies by Coats and Margulies (2006) for parietal (a) and occipital (b) bones and by Wang et al. (2014) for frontal (c) and parietal (d) bones, with (a) and (c) exhibiting larger elastic moduli than (b) and (d), respectively, both experimentally and as predicted by this growth model.

While these trends in measured modulus appear to agree with those of prior studies for the different skull bones, the localized accuracy of the resulting modulus would likely be improved with the integration of region-based expansion pressure information, such as that available for mouse models (Lee et al. 2019). Access to this sort of information, which could be potentially determined by leveraging high-resolution pediatric CT scans for individual patients over time to track region-level brain growth, would enable the skull growth process be captured more accurately and could simultaneously initiate more accurate strain distributions and growth patterns as a result.

In addition to leveraging more accurate growth pattern information, another way that this model could be improved is to have a better understanding of the strain thresholds contributing to growth, as well as the age-based modulus variation for a wider range of the pediatric population at a more regionalized level. Since it was difficult to assess strains and the resulting growth patterns in individuals under physiological conditions, a potential approach to enhancing the accuracy of this growth model could come from improving knowledge of the age-based variation in elastic modulus throughout the skull. Currently, little mechanical testing data exists for the pediatric population between the ages of 1 and 6-years old; additionally, test data was limited to specific locations on the skull due to the availability of experimental samples (Crandall et al. 2013). As a result, models often have to extrapolate to approximate age-based and region-based properties throughout the skull (Irwin & Mertz 1997). With greater understanding of age-based localized elastic modulus trends, the key significant growth parameters in this model (ε_{growth} , ε_{max} , and E_{24mos}) could be collectively tuned to better reflect the underlying elastic modulus found throughout the skull. This could potentially enable development of age-based and region-based modulus distribution functions.

Overall, access to region-based expansion information for the growing brain in combination with localized modulus information throughout the skull, both as a function of age, would enhance the biofidelity of this growth model through the aging process.

8.5. Bone Thickness

The initial configuration of this pediatric skull growth model contained localized thicknesses corresponding to the baseline FE model developed using the statistical model landmark coordinates. Applying prescribed growth to the skull, the thickness varied due to differences in strain distribution which affected regions of the skull differently. Sets of input parameters tended to correspond to different thickness distributions, as seen for the example simulation shown in Figure 8-6.



Figure 8-6: Skull thickness changes throughout the skull for a growth simulation demonstrating regional differences.

As determined from this computational growth model, different skull thicknesses as well as rates of skull thickness change occur for different regions of the skull. This finding generally agrees with the findings of prior studies. When taken collectively across prior studies, skull bone thickens during aging, with thickening rates varying depending on bone type (Crandall et al. 2013). Comparing between skull bones, frontal bone thickens at the slowest rate and occipital bone thickens at the greatest rate (Crandall et al. 2013). Additionally, combining the findings of prior studies, average thickness for the pediatric population is greatest for frontal bone and least for parietal bone (Crandall et al. 2013). Across all studies measuring pediatric skull thickness, though, a lack of appreciable samples and large variability prevents consistency in these findings, so it was best to consider general trends as opposed to age-specific measurements (Crandall et al. 2013).

8.5.1. Comparison Across All Simulations

A GLM was applied to the mean skull thickness predicted by this growth model for the final skull configuration to understand the differences in thickness distribution within the skull in response to the combination of input parameters implemented into the model. The results of this analysis are shown in Table 8-6 for all bones as well as for each individual skull bone in the model.

	All Bones	Frontal Bone	Parietal Bone	Occipital Bone
Intercept	2.38E+00**	2.48E+00**	2.19E+00**	2.76E+00**
ϵ_{growth}	-2.77E+02**	-2.80E+02**	-2.75E+02**	-2.81E+02**
ε _{max}	-3.00E+01*	-3.14E+01*	-2.83E+01*	-3.28E+01*
E _{24mos}	2.70E-04**	2.52E-04**	2.91E-04**	2.39E-04**
n _{fusion,font}	-	-1.02E-03*	-	-
<i>E</i> _{suture}	-	-	-	-
ε_{grow} : ε_{max}	1.21E+05**	1.21E+05**	1.21E+05**	1.20E+05**
ε_{grow} : E_{24mo}	-1.15E-01**	-1.12E-01**	-1.19E-01**	-1.10E-01**
ϵ_{grow} : n_{fus}	-	-	-	-
ε_{grow} : ε_{suture}	-	-	-	-
ε_{max} : E_{24mo}	-4.16E-02**	-3.88E-02**	-4.48E-02**	-3.64E-02**
ε_{max} : n_{fus}	-	-	-	-
$\boldsymbol{\varepsilon}_{max}$: $\boldsymbol{\varepsilon}_{suture}$	-	-	-	-
E_{24mo} : n_{fus}	-	-	-	-
E_{24mo} : ε_{suture}	-	-	-	-
n_{fus} : ε_{suture}	-	-	-	-

Table 8-6: Bone thickness GLM parameters (by row) including input parameter main effects and second-order interaction terms for all bones (Column 1) and individual bones (Columns 2-4).

(Units: mm) (* indicates p<0.05 and ** indicates p<0.001)

As seen in Table 8-6, each input parameter aside from ε_{suture} , the strain driving suture patency, and $n_{fusion,font}$, the predicted fontanelle closure age driving fontanelle growth, were significant contributors towards varying the bone thickness predicted by the model. Additionally, like that of bone modulus, the interaction of ε_{growth} and ε_{max} , both with each other and with E_{24mos} , were influential in driving thickness variation within the model. This was seen for the interaction plot for mean final bone thickness in Figure 8-7b, where the final bone thickness varies differently depending predominantly on the levels of growth and maximum strain as well as the predicted final modulus, seen through non-parallel lines for the plots of each of these inputs.

When visualized alongside the main effects plot (Figure 8-7a), the thickest mean final bone appears to occur when ε_{growth} and ε_{max} are minimized and E_{24mos} is maximized due to the growth process employed by this model, similar to bone modulus. Additionally, in comparison to modulus, it appears that the magnitude of thickening increases at a greater rate as the strain thresholds are reduced, as evidenced by the increase rate of thickness with the decrease of each of these parameters. This was likely attributed to the cubic factor of thickness growth used to relate moment of inertia to thickness for the model (Section 4.3.8).



Figure 8-7: Main effects plot (a) and interaction plot (b) of each input parameter on mean bone thickness across all bone elements in the final skull model.

8.5.2. Comparison Within Each Simulation

The one-way ANOVA test used to investigate differences in final mean bone thickness by bone type for each individual simulation suggests that significant differences exist between bone thickness for each simulation (Table 8-7). Investigating pairwise comparisons of bone thickness for each bone type reveals that each pairwise set of skull bones in the model possesses a significantly different thickness, similar to the findings for bone modulus (Table 8-7). For the final state of each simulation, it was found that occipital bone was thickest, frontal bone was second thickest, and parietal bone was thinnest.

The one-way ANOVA test assessing the difference in mean bone thickness change by bone type between the initial and final states for each individual simulation suggests that significant differences in thickness growth occurred in 174 of the 243 simulations (Table 8-7). Investigating pairwise comparisons for each bone type, significant differences in thickness growth magnitude occurred most often between parietal and occipital bone, second-most for frontal and parietal bone, and least often for frontal and occipital bone. In general, thickness change was greatest in parietal bone, second-greatest in frontal bone, and least in occipital bone.

Table 8-7: One-way ANOVA results and corresponding pairwise comparisons for mean final bone thickness and bone thickness growth magnitude by bone type within each individual growth simulation

Number of	Comparison	Significant	Pairwise Significance	
Simulations		ANOVA Tests	Comparison Group	Frequency
243	Final Bone Thickness	-	1) Frontal/Parietal	243
		2432) Frontal/Occipital3) Parietal/Occipital	243	
			3) Parietal/Occipital	243
	Bone		1) Frontal/Parietal	123
	Thickness Growth	174	2) Frontal/Occipital 84	84
			3) Parietal/Occipital	165

8.5.3. Implications of Findings for Bone Thickness

When viewing the effect of each input parameter on the resulting final bone thickness distribution predicted by the model, it appears that the thickest average model occurs for minimized strain thresholds and maximized predicted final modulus, while the thinnest average model occurs for the opposite case. Since each of these parameters and their interaction with one another were most influential towards altering the final thickness within the skull, and since each
parameter was significant within the GLM for skull thickness, these three parameters are potentially the most important towards directing skull thickness predicted by this growth model.

In agreement with prior studies investigating pediatric skull thickness, differences in final bone thickness were identified for parietal, frontal, and occipital bones in the model. Additionally, differences in bone thickness change were identified for a subset of growth simulations, specifically those with input parameter combinations resulting in the greatest final bone thicknesses.

While this model predicted a greater rate of thickening for parietal bone than frontal bone, it did not predict a greater rate for occipital bone than frontal and parietal bone, which was found in prior measurement studies (Crandall et al. 2013). Despite this difference, since prior studies involved measuring calvaria and averaging findings for specific age groups, the accuracy of these findings is potentially impacted by biological variability between subjects, so may not be representative of the pediatric population as a whole. Additionally, CT scans performed on pediatric individuals are inherently low quality to avoid radiation exposure, limiting the accuracy of thickness measurements. Having access to thickness information throughout the skull of an individual pediatric subject over time to track growth trends would likely enable more realistic thickness metrics for the pediatric population, potentially facilitating the development of predictive functions relating localized thickness to age.

To enhance the accuracy of this model in response to the mechanical strains initiated through growth simulations, several additional pieces of information could be leveraged. First, as noted for bone modulus, having access to region-based expansion information for the intracranial volume of pediatric subjects over time would enable the skull growth process to be captured more accurately. This is because having a more realistic expansion process would result in more accurate strain distributions and corresponding growth patterns experienced throughout the model.

In addition, another way that the model could be improved is to have a better understanding of the strain thresholds contributing to growth, and from this growth information, to understand the driving factors in the skull that contribute to thickness changes as opposed to modulus changes. This model was developed using the assumption that thickness growth occurs to a greater extent as the modulus increases by following a parameter, β , that varies linearly with increasing modulus (Section 6.2). However, this β -parameter is based on the finding that skull growth is predominantly modulus-based at young ages and is primarily thickness-based at older ages because the skull modulus approaches that of an adult, even though it is known that the skull advances in thickness at younger ages to some extent as well (Davis et al. 2011). By leveraging more accurate pediatric age-based thickness data in combination with age-based modulus data for individual pediatric subjects, the significant predictors of pediatric skull bone modulus and thickness growth, specifically ε_{growth} , ε_{max} , and E_{24mos} , in combination with the β -parameter, which divides growth between stiffness and thickness, could be collectively tuned so that the growth model better represents the elastic modulus and thickness distribution found throughout the skull.

Overall, the presence of region-based expansion data for the growing brain in combination with localized-resolution thickness and modulus information throughout the skull as a function of age, could collectively be used to better understand the strain distributions occurring throughout the skull and the corresponding variations in thickness and modulus that those strain distributions initiate. In doing this, the understanding of structural growth and the corresponding assignment of growth between stiffness and thickness could be performed more accurately in the model which would further increase its accuracy throughout the aging process.

8.6. Suture Width

The effective suture widths determined for the initial configuration of this pediatric skull growth model correspond to the widths of suture elements within the baseline FE model. Applying prescribed growth to the skull, effective suture width varied differently due to the strain distribution throughout the model, with a lack of appreciable strain corresponding to a reduction in suture width. Sets of input parameters tended to result in different suture width distributions within the model.

As seen in this growth model as well as in prior studies, different suture widths and rates of suture width change occur for the different sutures of the skull. When viewed across prior studies, suture width for all cranial sutures decreases with age, with the rates of decrease depending on the specific suture (Crandall et al. 2013; Idriz et al. 2015). Comparing between the primary skull sutures, the metopic suture is typically the first to fully close, which occurs during childhood (Idriz et al. 2015). Other primary sutures of the skull, specifically the sagittal, coronal, lambdoid, and squamous sutures, typically persist into adulthood before fusing completely, though their widths are sufficiently reduced so that they are no longer highly pliable fronts for skull growth by this point in time (Mitchell et al. 2011; Idriz et al. 2015). Despite these findings, the variability across studies and limited sample size only provides a general understanding of trends in suture width variation with aging for, as opposed to specific numeric measurements, for the pediatric population.

8.6.1. Comparison Across All Simulations

The final mean suture width predicted by this growth model was analyzed using a GLM to understand the differences in predicted suture width throughout the skull in response to the specific input parameters implemented into the model. The results of this analysis are seen in Table 8-8, both for all sutures combined and for each individually defined suture in the model.

secona-oraer interaction terms for all sutures (Column 1) and individual sutures (Columns 2-4).							
	All Sutures	<u>Metopic</u> Suture	<u>Sagittal</u> Suture	<u>Coronal</u> Suture	<u>Lambdoid</u> Suture	<u>Squamous</u> Suture	
Intercent	2 98E+00**	3 66E+00**	2 75E+00**	2 77E+00**	3 18E+00**	2 93E+00**	
E _{growth}	-1.33E+01	-1.01E+02**	-5.50E+00	-1.47E+01	-1.02E+01	1.33E+01	
ε_{max}	1.61E+00	-1.02E+01	3.98E+00	1.21E+00	4.72E+00	9.11E+00*	
E _{24mos}	-2.23E-06	5.74E-06	-3.67E-06	-2.59E-06	-4.33E-06	-5.64E-06	
n fusion,font	-	-	-	-	-	-	
$m{arepsilon}_{suture}$	-1.90E+02**	-3.05E+02**	-1.63E+02**	-1.87E+02**	-1.98E+02**	-1.05E+02**	
$\boldsymbol{\varepsilon}_{grow}$: $\boldsymbol{\varepsilon}_{max}$	-	-	-	-	-	-	
ε_{grow} : E_{24mo}	-	-	-	-	-	-	
$arepsilon_{grow}$: n_{close}	-	-	-	-	-	-	
$\boldsymbol{\varepsilon}_{grow}$: $\boldsymbol{\varepsilon}_{suture}$	-2.59E+04**	-	-2.93E+04**	-2.28E+04**	-3.10E+04**	-3.24E+04**	
ε_{max} : E_{24mo}	-	-	-	-	-	-	
$arepsilon_{max}$: n_{close}	-	-	-	-	-	-	
ε_{max} : ε_{suture}	-1.40E+04**	-1.19E+04**	-1.48E+04**	-1.38E+04**	-1.63E+04**	-1.31E+04**	
E _{24mo} : n _{close}	-	-	-	-	-	-	
E_{24mo} : ε_{suture}	9.70E-03**	8.84E-03*	1.02E-02**	1.00E-02**	1.06E-02**	7.84E-03**	
n_{fus} : $arepsilon_{suture}$	-	-	-	-	-	-	

Table 8-8: Suture width GLM parameters (by row) including input parameter main effects and second-order interaction terms for all sutures (Column 1) and individual sutures (Columns 2-4).

(Units: mm) (* indicates p<0.05 and ** indicates p<0.001)

As seen in Table 8-8, the only significant individual input parameter in the model towards varying suture width is ε_{suture} , which drives suture patency in the skull. In addition to this individual input parameter, the interaction of ε_{suture} with ε_{growth} , ε_{max} , and E_{24mos} were all influential in driving suture width variation within the model. When viewing the main effects plot for mean final suture width in Figure 8-8a, ε_{suture} variation is seen to be the largest driver of suture width change. When seen alongside the interaction plot for mean final suture width in Figure 8-8a.

8b, however, suture width does appear to vary to a different extent depending on the level of ε_{growth} , ε_{max} , and E_{24mos} , specifically for the larger individual levels of ε_{suture} .

In general, it appears that the minimum final suture width occurs with greater values of ε_{suture} and the maximum final suture width occurs with smaller values of ε_{suture} . This makes sense in the context of this growth model because larger values of ε_{suture} result in a greater likelihood of suture closure, since greater strains are required for sutures to remain in their current state (Section 6-4).

Additionally, the significant interaction terms with ε_{suture} (ε_{growth} , ε_{max} , and E_{24mos}) could potentially be significant due to their influence on the growth of bone elements proximal to suture elements, affecting the localized strain distributions and corresponding updates of those suture elements in the model. Specifically, at lower bone growth strain thresholds and higher predicted final bone moduli, each corresponding to increased bone growth, suture width closure occurs to a lesser extent, indicating that stiffer bone properties could potentially result in greater strains for neighboring suture elements and cause them to close to a lesser extent.



Figure 8-8: Main effects plot (a) and interaction plot (b) of each input parameter on mean suture width across all suture elements in the final skull model.

8.6.2. Comparison Within Each Simulation

The one-way ANOVA test investigating the differences in mean final suture width by suture type for each individual simulation suggests that significant differences exist between suture widths for each simulation (Table 8-9). Using Tukey post-hoc tests to investigate pairwise comparisons of suture width by type shows that several sutures consistently had significant width

differences, while several differed in a limited number of simulations (Table 8-9). In general, metopic, lambdoid, and squamous sutures possessed the greatest final widths, while sagittal and coronal sutures possessed the smallest final widths.

The one-way ANOVA test for mean suture width change by suture type for each individual simulation suggests that significant differences in suture width reduction magnitude occurred in 162 of the 243 simulations (Table 8-9). Investigating pairwise comparisons for suture type, significant differences in suture width change occurred most frequently between metopic suture and each other suture type, as well as between each other suture type and squamous suture. In general, the metopic suture closed with the greatest magnitude across all simulations. This was followed to a lesser extent by each of the other sutures, specifically the lambdoid, coronal, sagittal, and squamous, which demonstrated the smallest magnitude of closure across all simulations.

Table 8-9: One-way ANOVA results and corresponding pairwise comparisons for mean final suture width and suture width decrease magnitude by suture type within each individual growth simulation

Number of	Comparison	Significant	Pairwise Significance		
Simulations		ANOVA Tests	Comparison Group	Frequency	
	Final Suture Width	243	1) Metopic/Sagittal	243	
			2) Metopic/Coronal	243	
			3) Metopic/Lambdoid	81	
			4) Metopic/Squamous	103	
			5) Sagittal/Coronal	0	
			6) Sagittal/Lambdoid	243	
			7) Sagittal/Squamous	162	
			8) Coronal/Lambdoid	243	
			9) Coronal/Squamous	162	
242			10) Lambdoid/Squamous	69	
243	Suture Width Change	162	1) Metopic/Sagittal	162	
			2) Metopic/Coronal	162	
			3) Metopic/Lambdoid	162	
			4) Metopic/Squamous	162	
			5) Sagittal/Coronal	0	
			6) Sagittal/Lambdoid	32	
			7) Sagittal/Squamous	128	
			8) Coronal/Lambdoid	0	
			9) Coronal/Squamous	158	
			10) Lambdoid/Squamous	158	

8.6.3. Implications of Findings for Suture Width

Investigating the impact of each input parameter on the resulting final suture widths predicted by the model, the greatest final mean suture widths occur when ε_{suture} was minimized and the smallest final mean suture widths occur when ε_{suture} was maximized. Despite the significant interactions with ε_{growth} , ε_{max} , and E_{24mos} for the ε_{suture} parameter within the GLM for suture width, ε_{suture} appears to be the predominant driver of final suture width throughout the skull. Therefore, ε_{suture} is potentially the most important parameter towards directing suture width predicted by this growth model.

This model predicted a reduction in width for all sutures between the initial and final states of the model, which was consistent with the findings of biometric studies of age-based changes in suture width for the pediatric population (Crandall et al. 2013). Further, the model also predicted that the metopic suture would close at the greatest rate with aging, which was also observed in prior biometric studies (Crandall et al. 2013).

Despite this agreement, the accuracy of these findings, specifically in terms of the magnitude of closure of sutures, was likely limited by the inherent biological variability between subjects, since different individuals possess different suture widths at the same age. Having access to localized suture width information for an individual pediatric subject for all skull sutures during the aging process would likely enable more accurate suture width metrics for the pediatric population, potentially facilitating development of functions relating age to suture width closure for each suture in the skull.

In addition to accessing more accurate age-based suture width data, having access to region-based expansion information for the intracranial volume of individual pediatric subjects would correspond to more accurate strain distributions and corresponding spatial growth patterns experienced throughout the model, similar to bone modulus and thickness. By leveraging age-

based suture width and volume data for individual pediatric subjects, the model could be improved by enabling a better understanding of the strain thresholds corresponding to suture width maintenance for the different skull sutures. This information could then be used to tune ε_{suture} specifically for the each individual suture of the skull so that the accuracy of closure magnitudes could be enhanced in response to mechanical strain within the skull that is initiated during the growth process.

Overall, the presence of more localized suture width data in combination with region-based expansion information for the growing brain as a function of age could be collectively used to better understand the strain distributions occurring throughout the skull and their corresponding impact on suture width patency for each skull suture. In doing this, the current understanding of suture width variation in response to mechanical forces within the skull could be increased. This would likely facilitate increased accuracy of suture growth in the model throughout the aging process.

8.7. Parametric Analysis Summary

Validation of this pediatric computational growth model was performed using a full factorial experimental design by assessing the variations in the resulting model to five different input parameters, each with three levels, that contributed towards the growth of bone and fontanelle elements and the effective rate of closure of suture elements. The features of the model that were evaluated included the similarity of the model to age-based landmark geometric data, bone elastic modulus, bone thickness, and suture width. It was found that, in general, input parameters driving bone and suture growth were most influential towards informing the shape of the model, ε_{growth} , ε_{max} , and E_{24mos} were most important towards informing the elastic modulus and thickness of bone elements within the model, and ε_{suture} was most important towards

informing suture width within the model. As a result, each of these input parameters warrants further investigation for future development of this growth model.

In general, the growth trends observed for the model tended to agree with the findings of pediatric skull biometric and experimental property studies. Specifically, bone modulus spatial variations, bone thickness change variations, and suture width closure rates trended with those of prior studies. Despite this, however, the validity of these predictions is likely limited by the current availability of physiological data.

Greater availability of age-based material property and biometric data for the pediatric skull would likely provide greater insight into the accuracy of the model in its current form. Having access to ICV data alongside skull shape from a unified pediatric cranial dataset would be useful to better validate the growth shape of the skull. Additionally, more regionalized data regarding skull modulus and thickness as well as suture width could also enable improved validation of the structural growth patterns of the skull.

Moving forward, this model could be improved with information regarding the ICV growth pressures initiated by the expanding brain at a more localized spatial distribution. Implementing regionalized growth within the skull, as opposed to uniform growth throughout the entire skull, would likely initiate more accurate strain distributions throughout the model. From these localized strain distributions, especially with greater amounts of age-specific and localized pediatric skull structural property information, input parameters and update processes could be better adjusted so that the model optimally represents pediatric skull shape and structural patterns through the aging process.

8.8. Pediatric Skull Growth Model Application

The potential value and applicability of this pediatric cranial computational growth model lies in its ability to predict the shape and structural variations that occur throughout the skull during the aging process. In an idealized situation, after implementing an initial FE model containing a patient-specific morphology, the resulting cranial shape and structural features of the patient could be predicted for a future age. This is especially useful in the case of pathological conditions, where models containing planned surgical interventions could be incorporated and the long-term results could be simulated. In this section, this pediatric computational growth model developed here will be applied to predict the skull shape changes that are observed to occur with craniosynostosis.

8.8.1. Overview

Craniosynostosis is characterized by the premature fusion of one or more of the cranial sutures, as described in Section 2.3. In this section, the pathological condition of sagittal craniosynostosis, where the sagittal suture of the skull exhibits premature fusion, will be implemented into the initial baseline FE model and the resulting growth pattern will be analyzed. To simulate this condition, the initial bone modulus was assigned to the sagittal suture elements within the model. Additionally, the set of input parameters that resulted in the closest resemblance to the set of landmark statistical coordinates obtained from Li et al. (2015) from previous parametric analysis simulations will be employed (Table 8-10).

Input Parameter	Value	
ϵ_{growth}	1E - 4	
ε_{max}	1.5E - 3	
E _{24mos}	4 GPa	
$n_{fusion,font}$	24 months	
E _{suture}	1E - 3	

Table 8-10: Initial input parameters corresponding to the minimum growth model offset from the pediatric skull statistical landmark coordinates used for validation simulations.

After running the growth simulation, the resulting growth pattern of the craniosynostosis model was compared to that of the original model employing the same set of input parameters to investigate shape variations between the two. These model-to-model variations was compared to known variations between normal and sagittal craniosynostosis-afflicted individuals to assess the predictive capability of the growth model for this condition. Though exploratory in nature, performing this analysis demonstrated the potential utility of this growth model moving forward.

8.8.2. Results and Discussion

Investigating the growth shape variations between the original and sagittal craniosynostosis models, the craniosynostosis model exhibited differences from the original model in each anatomical plane (Figure 8-9). In the transverse plane, the craniosynostosis model predicted a slightly narrowed configuration in the anterior and posterior regions of the skull and an overall elongation of the skull in the anterior-posterior direction as compared to the original model (Figure 8-9a). In the coronal plane, the craniosynostosis model predicted a similar shape towards the base of the skull that becomes slightly narrower than the original model while moving in the superior direction, though this difference is relatively minimal (Figure 8-9b). Also, the final predicted height of the craniosynostosis model in the coronal plane was slightly less than that of the original model (Figure 8-9b). Finally, in the sagittal plane, the craniosynostosis model predicted an elongated shape as compared to the original model in the anterior-posterior direction (Figure 8-9c). Additionally, in the superior-inferior direction of the sagittal plane, the craniosynostosis model predicts a vertically stretched configuration at the anterior portion of the skull that transitions to a compressed configuration at the posterior portion of the skull in comparison to the original model (Figure 8-9c).



Figure 8-9: Cross-sections of the original and sagittal craniosynostosis-simulated models in the transverse (a), coronal (b), and sagittal (c) anatomical planes. For each plot, offsets between the models were magnified to emphasize relative differences.

Physiologically, it is known that cranial sutures act as fronts for bone growth (Katsianou et al. 2016). They experience mechanical stimuli such as strains due to pressure imparted by the expanding brain which correspondingly triggers growth of the skull surrounding the suture tissue (Katsianou et al. 2016). With craniosynostosis, however, the suture was fused and this front for

bone growth was eliminated, causing these straining and growth processes to be directed towards other regions of the skull where the sutures remain patent (Johnson & Wilkie 2011). Overcompensated growth in other skull regions results in a multitude of symptoms including irregular cranial growth patterns and raised intracranial pressure (Boulet et al. 2008, Johnson & Wilkie 2011). Specifically, sagittal craniosynostosis is characterized by narrowing and elongation of the skull in the transverse plane, narrowing of the skull in the coronal plane, and both elongation and skewing of the shape of the skull in the sagittal plane, as seen in Figure 8-10.



Figure 8-10: General variations in cranial shape between a normal skull (shown as dashed lines) and a sagittal craniosynostosis-afflicted skull in each anatomical plane (Adapted from Orthoamerica Products).

As compared to the understood differences between a normal pediatric skull and a pediatric skull exhibiting sagittal craniosynostosis, the general shape differences was captured fairly well in the transverse plane with elongation and narrowing, in the sagittal plane with a similar skew pattern and elongation, and to a slight extent in the coronal plane, with minimal narrowing at the apex of the skull (Figures 8-9 and 8-10). In accordance with the growth process employed by this model, for different growth patterns to occur, differences in strain distributions must arise during the growth process due to pressure imparted by the expanding ICV of the model. Due to simulated

fusion of the sagittal suture, mechanical strains were distributed to the other sutures of the model to a greater extent, directing expansion of the model towards those specific regions and consequently leading to the differences in cranial growth shape observed between the models.

Additionally, a common symptom of craniosynostosis is increased intracranial pressure, which occurs with the decreased expansion capability of the skull that results from a reduction in pliable suture material (Boulet et al. 2008; Johnson & Wilkie 2011). Comparing the pressures required to expand the ICV throughout the normal and craniosynostosis growth simulations, greater pressure is required throughout the entirety of the craniosynostosis case (Figure 8-11). For the growth process implemented in the model, with a reduction in suture material, greater intracranial pressure was required to expand the ICV by a given volume, which was observed within the craniosynostosis simulation as well as physiologically.



Figure 8-11: Plot of the original (blue) and craniosynostosis (red) model growth pressures by simulated age, which shows that greater pressure is required for the craniosynostosis model to expand the ICV by a given volume across all simulation iterations.

Despite expanding with a uniform pressure and not accounting for potential differences in ICV expansion region during the cranial growth process, the growth model still represents some of the underlying differences between the normal and craniosynostosis pediatric populations, both in terms of growth shape and raised intracranial pressure. The ability of the model to capture shape and intracranial pressure variations in response to alterations in the initial cranial structure highlights the importance of the differences in loading behavior of bone and suture elements in driving the growth shape and expansion pressure of the model.

In addition to differences in cranial growth shape, simulated sagittal craniosynostosis also results in slight differences in bone modulus and thickness. Though there is currently no available data to understand how craniosynostosis impacts these structural properties in neighboring bone tissue, this model suggests that, in general, both bone modulus and thickness are greater in the region surrounding the fused sagittal suture in the instance of craniosynostosis. This was because suture elements tend to take on a large portion of mechanical strain when present in a specific skull region, correspondingly limiting the strains experienced within neighboring bone elements. In the case of sagittal craniosynostosis, there were no longer suture elements in the sagittal region to bear this mechanical strain, causing bone elements in the region to experience greater strains which correspondingly increased their moduli and thicknesses to a greater extent. Though differences were found in the model, additional experimental study of pediatric cranial properties is needed to verify these findings.

8.8.3. Growth Model Application Summary

The pediatric computational growth model developed as part of this thesis was applied to assess its ability to predict the variations that occur within the skull in response to craniosynostosis. Though the model demonstrates the general growth variations that exist between normal and craniosynostosis-afflicted pediatric patients, it did not capture the variations with complete accuracy. That said, by providing a good approximate representation of the shape variations throughout the skull as well as the pressure differences and potential structural differences that occur with fusion of the sagittal suture through craniosynostosis, the growth model produced a valid preliminary understanding of the factors contributing to cranial growth as well as the impact of structural variations between otherwise identical models on the resulting cranial morphology. With the availability of further growth-related shape and structural data from future studies as well as more accurate ICV expansion information, the accuracy of the model can be further increased, allowing it to be applied to a wider variety of applications moving forward.

8.9. Pediatric Skull Growth Model Development Overall Conclusions

A computational growth model of the pediatric skull was developed and implemented to predict skull shape and material properties changes that result from the distribution of mechanical forces that occur during growth. The model was developed using an iterative framework, with each step corresponding to a discrete advancement in age. Starting with an initial baseline FE model of the pediatric skull, steps involved growth simulation by expanding the model ICV, analyzing the corresponding strain distribution induced throughout the model from the growth simulation, updating the shape and structural properties of the model in response to the strain distribution, and creating an updated model for the subsequent growth iteration.

After developing this growth model, it was validated using a full factorial experimental design by determining variations in model response to five different input parameters that were associated with different components of bone, fontanelle, and suture element growth that have not been widely-studied. It was found that each input parameter was a significant contributor towards the underlying growth shape of the model for different subsets of skull region, with an overall

shape more closely resembling that of landmark statistical points for smaller values of ε_{growth} and ε_{max} , corresponding to bone and fontanelle update thresholds, larger values of E_{24mos} , corresponding to the bone element update magnitude, and smaller values of ε_{suture} , corresponding to the strain required to maintain suture width. For bone elastic modulus and thickness, ε_{growth} , ε_{max} , and E_{24mos} were found to be the most significant, and for suture width, ε_{suture} was found to be the most significant.

Based on this validation, the model provides a good general understanding of the factors contributing to the underlying growth patterns of the skull. This was further shown by applying the model to simulate sagittal craniosynostosis and investigating the resulting growth patterns. In doing this, it was seen that the model was able to capture the general growth pattern variations that have been physiologically observed between normal and sagittal craniosynostosis-afflicted pediatric individuals.

Moving forward, the accuracy of this model could be enhanced with the availability of more consensus age-specific biometric and mechanical testing data regarding the bone moduli and thicknesses as well as the suture widths of the pediatric skull with aging at a more localized level and a wider spatial distribution throughout the skull. Additionally, an understanding of the localized ICV growth pressures induced within the skull could allow for more accurate strain distributions and corresponding improvements in model input parameters and update processes.

Overall, this pediatric skull growth model is an important tool that can be used in a preliminary sense to predict shape and structural variations that occur in response to aging. The model can provide insight into applications ranging from investigating the effect of pathological conditions on the growth pattern of the skull to developing patient-specific surgical approaches to improve long-term healing outcome. In its current state, the pediatric skull growth model developed here can act as a platform for future growth model development, which will be possible with wider availability of data moving forward.

CHAPTER 9: CONCLUSIONS

This chapter provides a summary of the work completed for this thesis. In addition, contributions of this research to the field will be addressed and limitations related to the methods and assumptions will be explained. Finally, the avenues for future research based on this thesis will be discussed.

9.1. Summary

The pediatric population is highly susceptible to developing craniofacial pathologies due to differences in structural and material characteristics in comparison to adults. Despite these differences, there is currently a lack of experimental data regarding the pediatric skull. Additionally, there has been limited insight into the growth patterns of the pediatric skull and the factors contributing to this underlying growth. As a result, surgical treatments for pediatric cranial conditions are based on methodologies and materials implemented for the adult population, resulting in undesired long-term outcomes.

The goals of this thesis were outlined in Chapter 1. Specifically, the primary goal of this thesis was to improve our understanding of the pediatric skull. This overarching goal gave rise to two primary questions. First, what are the mechanical properties of the pediatric skull under loading? Second, how can we predict pediatric skull growth patterns with aging? These questions were addressed through the two phases of this thesis: determination of the microstructural and mechanical properties of pediatric skull tissue and development of a tissue growth model and a computational framework to predict pediatric skull growth. These tasks were developed to contribute to the fields of experimental and computational biomechanics, specifically by providing insight into the pediatric population subset.

Chapter 2 outlined cranial anatomy, with a specific focus on the anatomy and development of the pediatric skull. Previous pediatric cranial bone experimental studies were summarized, and

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prior computational studies of the pediatric skull and cranial growth models were outlined. Due to the lack current knowledge regarding the pediatric skull, both in terms of its structural response under loading and its age-related growth, a need for a better comprehensive understanding of the pediatric skull, both in terms of mechanical properties and developmental patterns, was identified.

Part I of this thesis, consisting of Chapters 3-5, described the specimen preparation, microstructural analysis, and experimental testing components of the pediatric cranial bone analysis component of this thesis. This involved developing an analysis algorithm for microstructural data and designing and fabricating a four-point bending device for pediatric skull samples. After developing these tools, samples were prepared from pediatric craniosynostosis surgical specimens between 4 and 10 months of age, scanned using micro-CT, and mechanically tested to failure under four-point bending conditions. From this, mechanical properties including ultimate stress and strain as well as elastic modulus were determined, and a Ramberg-Osgood stress-strain relationship was fit to the stress-strain response of each sample. It was found that analyzing pediatric cranial bone using micro-CT, as opposed to assuming solid cross-sections, resulted in differences in measured mechanical properties. Additionally, it was found that the mechanical properties of pediatric skull bone are different than those of adult skull bone, with elastic moduli approximately three times less, ultimate stresses slightly less, and ultimate strains roughly five times greater.

Part II of this thesis, consisting of Chapters 6-8, presented the development and parametric analysis of a computational growth model for the pediatric skull. This model was developed to predict skull shape and structural changes that result from the distribution of mechanical forces occurring during the growth process. Initially, tissue-specific structural remodeling processes were developed for the structures of the pediatric skull, specifically bones, fontanelles, and sutures. These processes were based on physiological observations and involved updating tissue properties based on their mechanical strains. These tissue-specific growth processes were then incorporated into the individual elements of a pediatric skull FE model to simulate skull growth. To simulate the growth of the pediatric skull, the FE model was iteratively grown by expanding its internal volume, analyzing the corresponding strain distribution, updating the model based on that strain distribution in accordance with the tissue-specific structural remodeling processes, and creating a new model representing the subsequent growth state. A parametric analysis was then performed using this model with input parameters corresponding to the skull growth process to investigate their impact on the resulting shape and structural properties of the skull model. It was found that certain combinations of input parameters corresponded to a skull shape that more closely resembled a set of landmark coordinates developed from a pediatric cranial CT database and that differences in structural properties including bone modulus, bone thickness, and suture width depended on specific input parameter magnitudes. Finally, the model was applied to predict the physiologically-observed growth variations occurring with sagittal craniosynostosis. In assessing the resulting model, it was shown to be capable of predicting general shape variations and heightened intracranial pressures that occur with this pathological condition. The model validation and application processes highlighted the value of additional pediatric skull data towards improving the growth model moving forward.

9.2. Contributions

The contributions of this thesis are listed and described as follows:

1. Developed an experimental test rig and a custom four-point bending setup for pediatric cranial bone.

Many testing apparatuses available to test biological materials have either large loading force resolutions and large stroke lengths or small loading force resolutions and small stroke lengths. Due to the unique behavior of pediatric skull bone under loading, specifically low failure forces and large failure deformations, a testing apparatus with small measurement sensitivity and large stroke length was required. To meet this requirement, a custom testing apparatus was designed. This Arduino-controlled and linear actuator-driven device accommodates a range of input displacements while simultaneously enabling a range of input sensitivities with the installation of an applicable load cell. Test fixtures were made to be interchangeable for this apparatus so that it could accommodate a wide array of biological tests for future applications.

Many prior studies have tested pediatric cranial bone under three-point bending, subjecting the sample to point loading which can induce undesired effects. The custom-designed four-point bending setup that was implemented to test pediatric cranial bone was designed to ensure negligible shear forces and a near-constant moment across the sample during testing with the incorporation of a ball-and-socket loading head. This enabled a good understanding of the whole-sample loading response and correspondingly allowed for calculation of effective mechanical properties for tested samples.

2. Performed experimental tests on pediatric cranial bone.

Due to the difficulties associated with obtaining pediatric cranial tissue, there is very limited data concerning the mechanical properties of the pediatric skull, with the majority of data coming from pre-term infants. This study performed mechanical tests on 68 bone samples from 8 pediatric cranial specimens aging from 4 to 10 months. These tests contributed valuable insight to the behavior of pediatric cranial bone under loading within this age range and correspondingly enabled

calculation of effective mechanical properties which can be used to develop optimal pediatric surgical materials or to implement into pediatric cranial FE models.

3. Analyzed pediatric cranial bone microstructure.

While it is known that pediatric cranial bone develops a tri-layer structure with aging, no prior studies have sought to quantify this structure. Additionally, previous experimental efforts have approximated the cross section as solid, leading to potential inaccuracies in mechanical property data. This study used micro-CT to image the cross-sectional structure of pediatric cranial test samples. An analysis algorithm was then developed to process these images and to calculate microstructural properties for each sample. Using these calculated microstructural properties alongside experimental test data provided potentially enhanced mechanical property measurements for pediatric cranial test samples as opposed to assuming a solid cross section.

4. Developed a tissue-specific analytical model for the pediatric skull.

Currently, it is understood that biological growth stems from mechanical stimuli; however, there has been limited understanding as to how these growth-related stimuli contribute towards the underlying growth patterns observed in the developing pediatric skull. Since it was understood that different anatomical components within the pediatric skull, specifically bones, fontanelles, and sutures, develop differently with aging, this work involved developing specific analytical update methodologies for each of these components in response to growth. This was done by translating mechanical strain into material and cross-sectional growth of the individual tissues differently based on the current physiological understanding of each. While it is limited by the availability of current data, this analytical model provides insight into the different development

patterns associated with the different tissues of the pediatric skull and can be built upon through the findings of future studies.

5. Developed a computational framework for pediatric skull growth.

Currently, there has been limited investigation into the growth patterns of the pediatric skull, and no prior study has attempted to computationally model the pediatric skull shape and structural property changes that occur with aging. This work involved developing and implementing a computational model to investigate the growth patterns of the pediatric skull. Starting from an initial pediatric skull FE model, the growth structure employed an iterative framework with each iteration representing a discrete advancement in age. This allowed the model to predict the shape and structural makeup of the pediatric skull for any future age. Applications of this model include investigating the impact of pathological conditions on regular growth patterns as well as developing patient-specific surgical approaches to improve long-term healing outcomes. While it is limited in terms of the data available to inform the growth process, this model is intended to act as an initial framework that future growth models can build upon with the wider availability of data moving forward.

9.3. Limitations

This thesis contains several limitations related to both the experimental testing and growth model development efforts.

9.3.1. Experimental Limitations

One primary experimental limitation relates to the assumptions made regarding the calculated mechanical properties. Since the specific cross-sectional slice within the gauge length where sample failure occurred was unknown, the calculation method employed for mechanical

property measurement used the average geometric properties for each sample across all crosssectional slices within the gauge length, even though cross-sections with different geometric properties are subjected to different stresses under the same loading scenario. Despite this, however, the effective mechanical property measurements obtained here with consideration of localized microstructure are likely more accurate than those obtained assuming solid cross-section since the localized porosity within the bone structure is accounted for.

Another experimental limitation relates to the four-point bending setup used in this study. In some instances, during experimental testing, rotation of the ball-and-socked joint below the loading head occurred. This resulted in unequal forces at each of the contact points and different contact locations in relation to the sample, causing an unequal moment across the sample as well as the development of a shear force, both of which increase in magnitude as the ball-and-socket joint rotates to a greater extent. Despite these potential effects, in cases where rotation occurred, the magnitude of rotation was minimal prior to sample failure, resulting in a shear force that was essentially negligible. Additionally, since the sample was centered between the contact points and the distance between contact points was sufficiently large, the moment was effectively constant across the sample throughout the duration of testing.

A final experimental limitation stems from the test specimens obtained for the study. Since specimens were obtained from pediatric patients with craniosynostosis, they contained a fused sagittal suture which is not present in a healthy pediatric population. As a result, the specimens could potentially differ in structure from those of healthy individuals, especially if acquired adjacent to the fused suture tissue. To mitigate these potentially unrepresentative effects, samples were acquired at an offset from the fused sagittal suture to decrease the likelihood that the sample was influenced by the fused suture region. This strategy was likely sufficient because no effects of sample acquisition location, both in the anterior-posterior and lateral directions, were observed for calculation of mechanical and geometric properties within each test specimen.

9.3.2. Growth Model Development Limitations

One primary limitation related to the pediatric skull growth model relates to the lack of available data needed to inform the growth process. While it is known that mechanical stimuli, measured as mechanical strains, contribute to growth within the skull, it is currently unknown how those mechanical stimuli quantifiably correspond to growth. Because of this, assumptions were made regarding the growth process, specifically in terms of the strain thresholds used to initiate structural changes for bone, suture, and fontanelle elements, the specific magnitude of bone and fontanelle growth during aging steps, and the proportion of bone growth contributed towards increasing modulus or thickness. Despite this lack of available data related to the onset and magnitude of growth, in its preliminary state, the growth processes implemented in this model was based as closely as possible on currently available physiological data found in literature, and the corresponding sensitivity of the model to variations in these findings was investigated through validation studies. For future model iterations, with greater availability of data, focus could be transitioned towards predicting the underlying mechanisms of growth as opposed to empirical assignments of growth magnitude, giving the model greater predictive capability.

Another growth model limitation stems from the expansion process applied to the skull ICV to initiate growth. It is understood that cranial growth occurs due to outward expansion of the brain; additionally, it is known that the brain exhibits regional growth, expanding in different locations with different rates and pressures during the aging process. Despite this understanding, it is currently unknown specifically how the brain regionally expands with aging for pediatric individuals. Therefore, the growth process implemented in this model followed a function relating

whole-skull ICV to age that was obtained from a previous study (Abbott 2000) using an LS-Dyna airbag model that applied a uniform volumetric expansion of the ICV with equivalent pressure in all directions. As a result, though the magnitude of growth was likely appropriate, the regional accuracy of the growth process and the corresponding growth shape and structural patterns could likely be improved with access to regional-level ICV expansion pressure information.

A final limitation of this growth model relates to the available data used to validate the model. In terms of structural validation data, since there is such limited availability of pediatric experimental and biometric data, and because the pediatric population exhibits a large degree of inherent variability, it was infeasible to numerically compare predicted model outputs to literature values and to correspondingly determine optimal sets of input parameters to capture what is seen in the population. Therefore, only general trends in structural properties were determined in response to varying model input parameters. In terms of the statistical landmark validation data, while the final configuration of the model was compared to the landmark dataset corresponding to the same age, the pediatric CT database used to develop the landmark dataset was different than that used to produce the ICV versus age relationship that informed the model growth process. Due to the biological and developmental differences in pediatric individuals, it is unlikely that the ICV used for this growth model corresponds to the ICV of the patients used to construct the landmark dataset, limiting the comparability between the two. With a dataset containing both landmark points and ICV information from the same pediatric subjects, an ICV growth magnitude corresponding to what was observed from the landmark dataset could be applied to the model. Doing this, the differences between the model and the landmark points could be attributed specifically to shape-based growth differences, as opposed to both shape and volume differences, enabling a better understanding of the differences in the skull growth patterns between the two.

9.4. Future Research Directions

9.4.1. Experimental Efforts

While the eight mechanically-tested pediatric cranial specimens greatly contribute to the current body of data within the 4-month to 10-month age range, performing experimental tests and microstructural analysis on additional specimens, both within the tested age range and throughout the pediatric population age subset, would help to solidify the findings and potentially provide more insight into age-based pediatric material properties and structural variations.

These experimental tests were performed on fresh samples. To investigate the potential effects of testing fresh-frozen pediatric cranial specimens on measured properties, future tests could section specimens and keep one section fresh while freezing the other section prior to testing to understand the impact of the freeze-thaw process on loading response for pediatric cranial bone.

Tests performed here were conducted to failure under four-point bending. Another avenue to increase understanding of pediatric cranial bone under loading could involve loading-unloading tests. This would provide better insight into elastic and yield behavior of pediatric cranial bone and could potentially allow a definitive yield point in the loading response to be determined. In addition, different testing methods, such as tension or compression, could be performed to understand pediatric skull structural responses as well as fracture toughness and critical defect size under these loading methodologies.

Most importantly, by providing a better understanding of the mechanical properties and microstructural characteristics of pediatric cranial bone, the experimental efforts of this thesis can aid in the development of surgical tools, hardware, and materials that are optimally suited for the pediatric population. Implementing tools and materials that are compatible with the pediatric bone structure and mechanical characteristics identified through this work ensures appropriate treatments during procedures as well as positive long-term outcomes for pediatric patients.

9.4.2. Growth Model Development Efforts

The growth model developed here is intended to act as a platform for future model development. With greater availability of age-related and localized structural property and biometric data for the pediatric skull, as well as better knowledge of the region-level expansion pressures present throughout the ICV during the growth process, the accuracy of this model could be improved. Expanding the brain by applying regionalized pressures corresponding to age-specific growth patterns would induce more realistic strain distributions throughout the skull. From these strain distributions as well as improved knowledge of the age-specific variations in structural properties throughout the skull, growth update thresholds, parameters, and methodologies could be developed and implemented into the model that would accurately capture the growth process.

In addition, the validation processes for the model could be enhanced with unified datasets consisting of ICV, shape, and material property information obtained from the same group of pediatric subjects. This would enable a more comprehensive understanding of age-related development processes which would be valuable to assess the growth patterns demonstrated by the model.

Further, with greater availability of pediatric skull experimental and biometric data for future model versions, focus could be transitioned from determining the optimal update quantities, thresholds, and parameters for model growth, which are inherently empirical in nature, towards understanding the underlying mechanisms of bone, fontanelle, and suture growth at a physiological level. This would involve developing update methodologies for bone, fontanelle, or suture elements that independently represent what is seen in experimental and biometric data without relying on the data to inform them. Capturing the underlying physiological processes of cranial growth at a structural level would enable accurate predictions of model growth patterns for any

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specific cranial morphology during the aging process. This would give the model greater value and applicability towards understanding cranial growth patterns and processes at a patient-specific level moving forward.

Most importantly, with continued enhancement, the pediatric skull computational growth model developed in this thesis can contribute to the improvement of surgical planning procedures and pediatric surgical hardware. With a model that is able to predict the growth patterns of the pediatric skull, patient-specific FE models and pathological conditions could be implemented to determine the resulting growth pattern. Understanding the predicted growth pattern, different virtual procedures could be implemented into the model and the long-term growth patterns in response to those procedures could be explored to determine the procedure that results in the optimal long-term response. Additionally, this model could be used to develop surgical hardware that is compatible with the growing pediatric skull by implementing this hardware into the model and investigating the underlying growth pattern of the skull over time. Overall, with greater availability of pediatric skull data, an improved growth model could be developed that ensures the optimal surgical treatments are applied to pediatric surgical patients to maximize their future wellbeing moving forward.

REFERENCES

- A M Silau, B Fischer Hansen, & I Kjaer. (1995). Normal prenatal development of the human parietal bone and interparietal suture. *Journal of Craniofacial Genetics and Developmental Biology*, *15*(2), 81–86.
- Abbott, A., Netherway, D., Niemann, D., Clark, B., Yamamoto, M., Cole, J., Hanieh, A., Moore, M., & David, D. (2000). CT Determined Intracranial Volume for a Normal Population. *Journal of Craniofacial Surgery*, 11(3), 211–223.
- Arbogast, K. B., & Maltese, M. R. (2015). Pediatric Biomechanics. In The Medical College of Wisconsin Inc on behalf of Narayan Yoganandan, N. Yoganandan, A. M. Nahum, & J. W. Melvin (Eds.), *Accidental Injury* (pp. 643–696). Springer New York.
- Ashok, N., & Hu, J. (2018). Paediatric Head Injury Prediction: Investigation of Suture Material Properties. *IRCOBI*, 2.
- Bindeman, L. (2017). Thick Shell Element Form 5 in LS-DYNA. Livermore Software Technology.
- Boulet, S. L., Rasmussen, S. A., & Honein, M. A. (2008). A population-based study of craniosynostosis in metropolitan Atlanta, 1989–2003. *American Journal of Medical Genetics Part A*, 146A(8), 984–991.
- Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology*, *54*(1–3), 241–257.
- CDC. (2019, December 4). *Facts about Craniosynostosis / CDC*. Centers for Disease Control and Prevention. Retrieved January 9, 2020, from https://www.cdc.gov/ncbddd/birthdefects/craniosynostosis.html
- Chiba, F., Makino, Y., Motomura, A., Inokuchi, G., Torimitsu, S., Ishii, N., Sakuma, A., Nagasawa, S., Saitoh, H., Yajima, D., Hayakawa, M., Odo, Y., Suzuki, Y., & Iwase, H. (2013). Age estimation by multidetector CT images of the sagittal suture. *International Journal of Legal Medicine*, 127(5), 1005–1011.
- Coats, B., & Margulies, S. S. (2006). Material Properties of Human Infant Skull and Suture at High Rates. *Journal of Neurotrauma*, 23(8), 1222–1232.
- Coats, B., Margulies, Susan, & Ji, Songbai. (2007). Coats2007-parametric study of head impact in the infant.pdf. *Stapp Car Crash Journal*, *51*, 1–15.

Coelho, P. G., Fernandes, P. R., Rodrigues, H. C., Cardoso, J. B., & Guedes, J. M. (2009). Numerical modeling of bone tissue adaptation—A hierarchical approach for bone apparent density and trabecular structure. *Journal of Biomechanics*, 42(7), 830–837.

Crandall, J. R. (Ed.). (2013). Pediatric injury biomechanics: Archive & textbook. Springer.

- Davis, M. T., Loyd, A. M., Shen, H. H., Mulroy, M. H., Nightingale, R. W., Myers, B. S., & Bass, C.
 D. (2012). The mechanical and morphological properties of 6 year-old cranial bone. *Journal of Biomechanics*, 45(15), 2493–2498.
- Dobson, A., & Barnett, A. (2008). An Introduction to Generalized LInear Models (3rd ed.). Taylor & Francis.
- Elizabeth Lajeunie, Martine Le Merrer, Catherine Bonaiti-Pellie, D Marchac, & Dominique Renier. (1995). Genetic study of nonsyndromic coronal craniosynostosis. *American Journal of Medical Genetics*, 55(4), 500–504.
- Frieden, T. R., Ikeda, R., & Hunt, R. C. (2010). Traumatic Brain Injury in the United States. 74.
- Gerhard, F. A., Webster, D. J., van Lenthe, G. H., & Müller, R. (2009). In silico biology of bone modelling and remodelling: Adaptation. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 367(1895), 2011–2030.
- Giordano, C., & Kleiven, S. (2016). *Development of a 3-Year-Old Child FE Head Model, Continuously Scalable from 1.5- to 6- Year-Old.* 15.
- Goos, J. A. C., & Mathijssen, I. M. J. (2019). Genetic Causes of Craniosynostosis: An Update. *Molecular Syndromology*, 10(1–2), 6–23.
- Haug, R. H., & Foss, J. (2000). Maxillofacial injuries in the pediatric patient. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 90(2), 126–134.
- Huelke, D. F. (n.d.). An Overview of Anatomical Considerations of Infants and Children in the Adult World of Automobile Safety Design. 21.
- Idriz, S., Patel, J. H., Ameli Renani, S., Allan, R., & Vlahos, I. (2015). CT of Normal Developmental and Variant Anatomy of the Pediatric Skull: Distinguishing Trauma from Normality. *RadioGraphics*, 35(5), 1585–1601.
- Irwin, A., & Mertz, H. J. (1997). Biomechanical basis for the CRABI and Hybrid III child dummies. *SAE Technical Paper 973317*.

- Johnson, D., & Wilkie, A. O. M. (2011). Craniosynostosis. European Journal of Human Genetics, 19(4), 369–376.
- Katsianou, M. A., Adamopoulos, C., Vastardis, H., & Basdra, E. K. (2016). Signaling mechanisms implicated in cranial sutures pathophysiology: Craniosynostosis. *BBA Clinical*, *6*, 165–176.
- Klinich, K. D., Hulbert, G. M., & Schneider, L. W. (2002). Estimating Infant Head Injury Criteria and Impact Response Using Crash Reconstruction and Finite Element Modeling. *Stapp Car Crash Journal*, 32.
- Kriewall, Timothy J. (1982). Structural, Mechanical, and Material Properties of Fetal Cranial Bone. Am. J. Obstet. Gynecol., 143(6), 707–714.
- Lee, C., Richtsmeier, J. T., & Kraft, R. H. (2019). A coupled reaction-diffusion-strain model predicts cranial vault formation in development and disease. *Biomechanics and Modeling in Mechanobiology*, 18(4), 1197–1211.
- Li, Z., Park, B.-K., Liu, W., Zhang, J., Reed, M. P., Rupp, J. D., Hoff, C. N., & Hu, J. (2015). A Statistical Skull Geometry Model for Children 0-3 Years Old. *PLOS ONE*, *10*(5), e0127322.
 Libby, J., Marghoub, A., Johnson, D., Khonsari, R. H., Fagan, M. J., & Moazen, M. (2017).
 Modelling human skull growth: A validated computational model. *Journal of The Royal Society Interface*, *14*(130), 20170202.
- Louise Scheuer, & Sue Black. (2004). The Juvenile Skeleton (1st ed.). Elsevier/Academic Press.
- Loyd, A. (2011). The structural, inertial, geometric and mechanical properties of the pediatric head, PhD Dissertation, Duke University.
- Lumen Learning. (n.d.). *The Bones of the Skull | Human Anatomy and Physiology Lab (BSB 141)*. Lumen Learning. Retrieved February 25, 2020, from https://courses.lumenlearning.com/ap1x94x1/chapter/the-bones-of-the-skull/
- Marcus, J. R., Domeshek, L. F., Loyd, A. M., Schoenleber, J. M., Das, R. R., Nightingale, R. W., & Mukundan, S. (2009). Use of a Three-Dimensional, Normative Database of Pediatric Craniofacial Morphology for Modern Anthropometric Analysis: *Plastic and Reconstructive Surgery*, 124(6), 2076–2084.
- Margulies, S. S. (2000). Infant Skull and Suture Properties: Measurements and Implications for Mechanisms of Pediatric Brain Injury. *Journal of Biomechanical Engineering*, 122(4), 364.

- Mayo Clinic. (n.d.). *Craniosynostosis—Symptoms and causes*. Mayo Clinic. Retrieved January 9, 2020, from <u>https://www.mayoclinic.org/diseases-conditions/craniosynostosis/symptoms-causes/syc-20354513</u>
- McPherson, G. K., & Kriewall, T. J. (1980). The elastic modulus of fetal cranial bone: A first step towards an understanding of the biomechanics of fetal head molding. *Journal of Biomechanics*, *13*(1), 9–16.
- Mitchell, L. A., Kitley, C. A., Armitage, T. L., Krasnokutsky, M. V., & Rooks, V. J. (2011). Normal Sagittal and Coronal Suture Widths by Using CT Imaging. *American Journal of Neuroradiology*, 32(10), 1801–1805.
- Motherway, J. A., Verschueren, P., Van der Perre, G., Vander Sloten, J., & Gilchrist, M. D. (2009). The mechanical properties of cranial bone: The effect of loading rate and cranial sampling position. *Journal of Biomechanics*, 42(13), 2129–2135.
- Mullender, M. G., & Huiskes, R. (1995). Proposal for the regulatory mechanism of Wolff's law. *Journal* of Orthopaedic Research, 13(4), 503–512.
- NIST. (n.d.). *Full factorial example*. Engineering Statistics Handbook. Retrieved February 19, 2020, from https://www.itl.nist.gov/div898/handbook/pri/section4/pri471.htm
- Opperman, L. A. (2000). Cranial sutures as intramembranous bone growth sites. *Developmental Dynamics*, 219(4), 472–485.
- Orthoamerica Products. (n.d.). *What is Craniosynostosis?* STARband. Retrieved February 26, 2020, from https://www.starbandkids.com/plagiocephaly-blog/what-is-craniosynostosis
- P Prasad, & J W Melvin. (1985). Review of biomechanical impact response and injury in the automotive environment. *Task B Final Report. Ann Arbor: Transportation Research Institute*.
- Prange, M. T., Luck, J. F., Dibb, A., Ee, C. A. V., Nightingale, R. W., & Myers, B. S. (2004). Mechanical Properties and Anthropometry of the Human Infant Head. *Stapp Car Crash Journal*, 21.
- Roth, S., Raul, J.-S., & Willinger, R. (2010). Finite element modelling of paediatric head impact: Global validation against experimental data. *Computer Methods and Programs in Biomedicine*, 99(1), 25–33.
- Roth, S., Vappou, J., Raul, J.-S., & Willinger, R. (2009). Child head injury criteria investigation through numerical simulation of real world trauma. *Computer Methods and Programs in Biomedicine*, 93(1), 32–45.

- Ruimerman, R., Hilbers, P., van Rietbergen, B., & Huiskes, R. (2005). A theoretical framework for strain-related trabecular bone maintenance and adaptation. *Journal of Biomechanics*, 38(4), 931– 941.
- Soboleski, D., Mussari, B., & McCloskey, D. (1998). High-resolution sonography of the abnormal cranial suture. *Pediatric Radiology*, 28, 79–82.
- Wang, J., Donghua Zou, Zhengdong Li, Ping Huang, Dongri Li, Yu Shao, Huijun Wang, & Yijiu Chen. (2014). Mechanical Properties of Cranial Bones and Sutures in 1–2-Year-Old Infants. *Medical Science Monitor*, 20, 1808–1813.
- Weinans, H., Huiskes, R., & Grootenboer, H. J. (1992). The behavior of adaptive bone-remodeling simulation models. *Journal of Biomechanics*, 25(12), 1425–1441.
- Winkelstein, B. A. (2013). Orthopaedic Biomechanics (1st ed.). Taylor & Francis.Yuan, B., Goldman, R. N., Wang, E., Olorunnipa, O., & Khechoyan, D. Y. (2016). Generating a

3D Normative Infant Cranial Model. Procedia Computer Science, 80, 988–998.
APPENDIX A: TABLE OF ALL PRIOR PEDIATRIC SKULL EXPERIMENTAL DATA

		Specimen			Mechanical Property						
<u>Author</u> (Year)	Testing Ag Method (mon	<u>Age</u> (months)	<u>Bone</u>	<u>Orientatio</u> <u>n (Suture)</u>	<u>Elastic</u> <u>Modulus</u> (MPa)	<u>Elastic</u> <u>Modulu</u> <u>s SD</u>	<u>Ultimate</u> <u>Stress</u> (MPa)	<u>Ultimat</u> <u>e Stress</u> <u>SD</u>	Ultimate Strain (%)	<u>Ultimat</u> <u>e Strain</u> <u>SD</u>	<u>Number</u> <u>of</u> Samples
				Parallel (Sagittal)	1.74	0.59	XXX	ххх	xxx	XXX	3
		0	Parietal	Perpendic ular (Sagittal)	4.01	1.28	ххх	ххх	ххх	ххх	3
			Frontal	Parallel (Coronal)	1.70	0.79	ххх	ххх	xxx	ххх	2
				Perpendic ular (Coronal)	3.05	0.88	ххх	ххх	ххх	ххх	2
				Parallel (Sagittal)	0.84	0.19	ххх	ххх	ххх	ххх	8
		-0.5	Parietal	Perpendic ular (Sagittal)	4.24	0.73	ххх	ххх	ххх	ххх	9
			Parietal	Parallel (Sagittal)	0.18	0.03	ххх	ххх	xxx	xxx	3
McPherson & Kriewall		-2.9		Perpendic ular (Sagittal)	0.94	0.41	ххх	ххх	ххх	ххх	10
		-3.4	Parietal	Parallel (Sagittal)	0.12	0.01	ххх	xxx	xxx	xxx	3
	3-Point Bending			Perpendic ular (Sagittal)	1.30	0.60	ххх	ххх	ххх	ххх	8
(1980)		-2.7	Parietal	Parallel (Sagittal)	0.14	0.08	XXX	ххх	xxx	xxx	5
				Perpendic ular (Sagittal)	3.62	0.46	ххх	ххх	ххх	ххх	5
		0	Parietal	Parallel (Sagittal)	0.57	0.14	XXX	xxx	XXX	XXX	5
				Perpendic ular (Sagittal)	3.72	0.35	ххх	ххх	ххх	ххх	5
				Perpendic ular (Sagittal)	3.30	0.64	ххх	ххх	ххх	ххх	5
			Frontal	Perpendic ular (Coronal)	2.83	0.96	ххх	ххх	ххх	ххх	5
				Perpendic ular (Coronal)	3.29	0.71	ххх	ххх	ххх	ххх	5
		72	Parietal	Parallel (Sagittal)	7.38	0.84	ххх	ххх	ххх	ххх	6
				Perpendic ular (Sagittal)	5.86	0.69	ххх	ххх	ххх	ххх	6
	Whole-			Parallel (Sagittal)	1740	xxx	ххх	ххх	xxx	ххх	1
Kriewall (1982)	Bone Flexion	Bone 0.0 lexion	Parietal	Perpendic ular (Sagittal)	4010	ххх	ххх	ххх	ххх	ххх	1

Table A-1: All prior pediatric skull experimental data containing author, testing method, bone type, sample orientation, number of samples tested, and results.

				Parallel (Sagittal)	870	ххх	ххх	ххх	ххх	ххх	1
		-0.5	Parietal	Perpendic ular (Sagittal)	4240	ххх	ххх	ххх	ххх	ххх	1
		-2.9	Parietal	Parallel (Sagittal)	180	xxx	ххх	xxx	xxx	xxx	1
				Perpendic ular (Sagittal)	940	ххх	ххх	ххх	ххх	ххх	1
				Parallel (Sagittal)	120	xxx	ххх	xxx	xxx	xxx	1
		-3.4	Parietal	Perpendic ular (Sagittal)	1300	ххх	ххх	ххх	ххх	ххх	1
				Parallel (Sagittal)	140	ххх	ххх	ххх	ххх	ххх	1
		-2.7	Parietal	Perpendic ular (Sagittal)	3620	ххх	ххх	ххх	ххх	ххх	1
				Parallel (Sagittal)	3300	xxx	ХХХ	xxx	xxx	xxx	1
		0.0	Parietal	Perpendic ular (Sagittal)	3720	ххх	ххх	ххх	ххх	ххх	1
		0.0	Parietal	Perpendic ular (Sagittal)	2961	ххх	ххх	ххх	ххх	ххх	1
		0.0	Parietal	Parallel (Sagittal)	1684	ххх	ххх	ххх	ххх	ххх	1
				Perpendic ular (Sagittal)	3594	ххх	ххх	ххх	xxx	ххх	1
		-1.4	Parietal	Parallel (Sagittal)	1646	ххх	ххх	ххх	ххх	ххх	1
				Perpendic ular (Sagittal)	3390	ххх	ххх	ххх	ххх	ххх	1
				Parallel (Sagittal)	1626	xxx	ХХХ	xxx	xxx	xxx	1
		-2.3	Parietal	Perpendic ular (Sagittal)	3634	ххх	ххх	ххх	ххх	ххх	1
				Parallel (Sagittal)	1044	xxx	ХХХ	xxx	xxx	xxx	1
	-2.3	Parietal	Perpendic ular (Sagittal)	3478	ххх	ххх	ххх	ххх	ххх	1	
	0.5 F	Parietal	Perpendic ular (Sagittal)	7360	ххх	ххх	ххх	ххх	ххх	1	
	-0.2	Parietal	Perpendic ular (Sagittal)	4301	ххх	ххх	ххх	ххх	ххх	1	
		0.0	Parietal	Parallel (Sagittal)	1434	ХХХ	ххх	ХХХ	ХХХ	ХХХ	1
				ular (Sagittal)	5167	ххх	ххх	ххх	ххх	ххх	1
		-1.6	Parietal	Parallel (Sagittal)	1996	ххх	ххх	ххх	ххх	ххх	1

				Perpendic ular (Sagittal)	3029	ххх	ххх	ххх	ххх	ххх	1	
				Parallel (Sagittal)	1238	ххх	ххх	ххх	ххх	xxx	1	
		-4.5	Parietal	Perpendic ular (Sagittal)	4232	ххх	ххх	ххх	ххх	ххх	1	
		-3.4	Parietal	Parallel (Sagittal)	57.70	19.66	4.25	0.35	xxx	XXX	2	
Margulies & Thibault (2000)	3-Point	-2.3	Parietal	Parallel (Sagittal)	404.34	190.87	11.02	5.43	ххх	ххх	5	
	Bending	0.2	Parietal	Parallel (Sagittal)	820.90	ххх	10.60	ххх	xxx	ххх	1	
		6	Parietal	Parallel (Sagittal)	2641.30	673.79	52.80	16.42	xxx	xxx	4	
		-4.4	Occipit al	Parallel (Lambdoid)	181.10	ххх	12.50	ххх	6.27	ххх	1	
		-2.7	Occipit al	Parallel (Lambdoid)	45.30	ххх	8.80	ххх	0.71	ххх	1	
		-2.7	Occipit al	Parallel (Lambdoid)	111.15	30.76	11.05	1.77	0.235	0.04949 7475	2	
				Parietal	Parallel (Sagittal)	85.15	49.43	5.55	0.07	0.63	0.36769 5526	2
		-1.8	Occipit al	Parallel (Lambdoid)	58.70	ххх	3.30	ххх	4.16	ххх	1	
		-1.4	Parietal	Parallel (Sagittal)	552.90	xxx	81.10	ххх	0.45	XXX	1	
		-1.1	Parietal	Parallel (Sagittal)	97.00	XXX	7.00	ххх	0.26	XXX	1	
		-0.5	Occipit al	Parallel (Lambdoid)	369.05	111.79	22.00	13.29	6.01	1.89504 6174	2	
Coats &	3-Point	3-Point -0.2	Occipit al	Parallel (Lambdoid)	220.20	12.87	7.05	0.49	4.235	1.09601 5511	2	
(2006)	Bending		Parietal	Parallel (Sagittal)	593.50	480.27	19.70	17.11	3.475	1.18086 8325	2	
		0.6	Parietal	Parallel (Sagittal)	336.80	ххх	37.80	ххх	14.9	xxx	1	
	0.7	Occipit al	Parallel (Lambdoid)	533.45	24.40	5.20	0.85	0.965	0.40305 0865	2		
			Parietal	Parallel (Sagittal)	182.70	xxx	8.40	ххх	4.5	xxx	1	
		1	Occipit al	Parallel (Lambdoid)	449.20	ххх	18.50	ххх	4.65	ххх	1	
			Parietal	Parallel (Sagittal)	815.50	XXX	53.70	ххх	7.53	XXX	1	
		1.5	Occipit al	Parallel (Lambdoid)	43.15	20.58	11.10	3.39	0.535	0.20506 0967	2	
		1.5	Parietal	Parallel (Sagittal)	490.63	107.14	24.97	4.98	6.24	0.84504 4378	3	
		1.8	Occipit al	Parallel (Lambdoid)	421.40	ххх	15.10	ххх	3.14	ххх	1	
		2.0	Parietal	Parallel (Sagittal)	409.90	159.10	20.65	9.12	6.4	1.76776 6953	2	

		2.3	Occipit al	Parallel (Lambdoid)	186.25	0.21	4.40	1.84	2.635	0.06363 961	2
		3.0	Occipit al	Parallel (Lambdoid)	890.55	603.94	34.75	12.23	3.55	1.42835 5698	2
			Parietal	Parallel (Sagittal)	1155.20	xxx	69.70	xxx	8.07	XXX	1
		4.5	Occipit al	Parallel (Lambdoid)	355.25	53.10	17.95	2.19	5.4	0.02828 4271	2
			Parietal	Parallel (Sagittal)	552.40	XXX	23.70	xxx	5	XXX	1
		11.0	Occipit al	Parallel (Lambdoid)	462.50	198.56	27.45	14.35	0.305	0.00707 1068	2
			Parietal	Parallel (Sagittal)	678.40	xxx	50.45	xxx	0.33	xxx	2
		12.0	Occipit al	Parallel (Lambdoid)	363.00	366.00	13.70	10.61	10.755	7.60139 7898	2
	Davis et al. 4-Point (2011) Bending		Parietal	Parallel (Sagittal)	383.65	xxx	35.40	xxx	10.765	xxx	2
		13.0	Parietal	Parallel (Sagittal)	216.80	xxx	15.10	xxx	8.85	xxx	1
			Frontal /Tri- Layer	Perpendic ular (Coronal)	4273.33	858.41	90.91	20.04	3.095	0.96359 2237	6
Davis et al. (2011)		4-Point Bending 72.0	Parietal /Tri- Layer	Perpendic ular (Sagittal)	3401.67	793.04	77.79	21.75	3.25166 6667	0.65522 839	11
		Parietal /Cortica I	Perpendic ular (Sagittal)	9870.00	1240.00	184.49	25.19	3.05	0.89	7	
Wang et al.	3-Point	18 +/- 6 (n=7)	Frontal	Perpendic ular (Coronal)	1265.65	120.90	99.75	11.08	9.72	4.24	14
(2014) Bendi	Bending	18 +/- 6 (n=7)	Parietal	Perpendic ular (Sagittal)	1103.01	112.77	87.12	10.58	8.66	2.7	14

APPENDIX B: MAXIMUM TISSUE UPDATE PROPORTIONS

Bone Tissue Bending Stiffness Growth Proportion ($\Delta EI_{max,bone}$)

The maximum bending stiffness update proportion for all bone tissue in the model, $\Delta EI_{max,bone}$, was developed using physiological data for both the elastic modulus and thickness of bone at the initial and final ages of the growth model (6-months and 2-years for this model) as well as the duration of the growth process (1.5 years, or 78 weeks). In doing this, the update proportion approximates the expected proportion of combined skull stiffening and thickening that would occur for a single growth iteration between 6-months and 2-years of age assuming a constant linear increase in growth throughout that age span.

This bending stiffness update amount, $\Delta EI_{max,bone}$, was calculated using the Equations A-1-3, which requires the elastic modulus and mean skull thickness at the initial and final model ages $(E_{start}, t_{start}, E_{end}, \text{ and } t_{end})$ as well as the duration of the growth process in weeks (n_{weeks}) . These findings, shown in Table A-2, were determined by considering the findings of this thesis alongside the values found in prior experimental studies. The final age modulus values were considered variable input parameters for model assessment that were interchanged between different simulation iterations because bone properties at this age have not been experimentally studied. Based on the assumption that the model possesses a rectangular cross section through its thickness, a cubic factor is used to associate thickness to moment of inertia. This is described in greater detail in Appendix C.

Table A-2: Input properties used for calculation of $\Delta EI_{max,bone}$ used for bone element growth.

Input Property	Initial Age (6mos)	Final Age (24mos)			
Modulus, <i>E</i> (GPa)	1.5	[2 3 4]			
Thickness, t (mm)	2.578	3.944			
Growth Weeks, <i>n_{weeks}</i>	78 weeks (18 months)			

 $\Delta EI_{max,bone}$ was calculated as a proportion of increase in the initial elastic modulus and moment of inertia for a single growth iteration (Equations A-1-A-3). This maximum update proportion, $\Delta EI_{max,bone}$, was kept constant throughout all simulation iterations.

$$\Delta E_{max} = \left(1 + \frac{\left(\frac{E_{end} - E_{start}}{E_{start}}\right)}{n_{weeks}}\right)$$
(A-1)

$$\Delta I_{max} = \left(1 + \frac{\left(\frac{t_{end} - t_{start}}{t_{start}}\right)}{n_{weeks}}\right)^3 \tag{A-2}$$

$$\Delta E I_{max,bone} = \Delta E_{max} * \Delta I_{max}$$
(A-3)

Maximum Fontanelle Tissue Bending Stiffness Growth Proportion ($\Delta EI_{max,font}$)

To enable fontanelle tissue to stiffen more rapidly than bone tissue, it was assigned an initial bending stiffness update proportion, defined as $\Delta EI_{max,font}$, which depended on the initial fontanelle modulus, E_{font} , the initial bone modulus, E_0 , and the predicted duration of time for fontanelle to fuse to bone, n_{fusion} , all shown in Table A-2. This update proportion was established by approximating the expected amount of fontanelle stiffening that would occur for a single growth iteration for the fontanelle element to fully ossify during the predicted time interval, assuming a constant linear increase in exclusively stiffening during that period of time, since fontanelle does not thicken when it is present. Since the duration of time required for fontanelle to fuse is not well defined, the growth period duration was treated as a variable input parameter. This calculation is outlined in Equation A-4.

Input Property	Initial Age (6mos)	Final Age (24mos)			
Modulus, E (GPa)	$8.315 * 10^{-3}$	1.5			
Growth Months, n_{fusion}	[12 24 36]				

Table A-3: Input properties used for calculation of $\Delta EI_{max,font}$ used for fontanelle element growth.

$$\Delta EI_{max,font} = \left(1 + \frac{\left(\frac{E_0 - E_{font}}{E_{font}}\right)}{n_{fusion}}\right)$$
(A-4)

Maximum Suture Width Closure Proportion (Δw_{max})

The maximum closure amount for all suture elements in the model, Δw_{max} , was determined using physiological data for suture widths at the initial age (6 months) and final age (2 years) of the growth model, w_{start} and w_{end} , respectively, acquired from the CT-based pediatric skull statistical model developed by Li et al. (2015), as well as the duration of the growth process (n_{weeks}) . This update amount, calculated in Equation A-5, is a negative value that represents the expected proportion of suture closure that would occur for a single growth iteration, assuming a constant linear decrease in suture width during the timespan of the growth captured in the simulation.

$$\Delta w_{max} = \left(1 + \frac{\left(\frac{w_{end} - w_{start}}{w_{start}}\right)}{n_{weeks}}\right)$$
(A-5)

APPENDIX C: RELATIONSHIP BETWEEN GEOMETRIC GROWTH ELEMENT THICKNESS

Thickness growth in the model is applied by updating the thickness of node pairs for the specific element. To associate a change in the moment of inertia of an element, I_{i+1} , to the thickness growth, t_{i+1} , involves assuming a rectangular cross section where the proportion of the cross section corresponding to non-structural area, α , is constant between iterations, as shown in Equation A-6. Inserting this expression into the moment of inertia update formula (Equation A-7) and simplifying gives the result shown in Equation A-8. Finally, by solving for the updated thickness, t_{i+1} , the relation between moment of inertia update proportion and nodal thickness is obtained (Equation A-9). This relationship between the moment of inertia and the nodal thickness was used to update nodal thicknesses in the model.

$$I = \frac{1}{12}b(1-\alpha)t^3$$
 (A-6)

$$I_{i+1} = I_i * (1 + \Delta I_{update}) \qquad (A-7)$$

$$t_{i+1}^3 = t_i^3 * (1 + \Delta I_{update})$$
 (A-8)

$$t_{i+1} = t_i^{3} \sqrt{1 + \Delta I_{update}} \qquad (A-9)$$

APPENDIX D: GROWTH MODEL ORGANIZATIONAL STRUCTURE, MODEL SETUP, AND OUTPUT PROCESSING USING MATLAB

This computational growth model was developed within MATLAB using a specific organizational structure. The model was run using the parallel computing feature in MATLAB which enabled execution of multiple growth simulations simultaneously on multiple workers using a parallel for loop, or "parfor," execution method. Within each parfor iteration, appropriate files with unique sets of input parameters were generated prior to running each simulation. This file structure, shown in Figure A-1, is described in detail in the remainder of this section.



Figure A-1: The file structure implemented for the pediatric skull growth model.

Within the main folder containing all files and simulations, there were two folders, "00_Base_Files/" and "01_Simulations/", and three MATLAB files. The entire simulation framework was controlled using the file "Pre_Simulation_Manager.m," which defined all input parameters and configured each individual growth simulation with the proper set of these input parameters. The other MATLAB files, "Build_Simulation.m" and "Run_Simulation.m", were required for establishing the specific folders for each simulation and executing each iterative growth simulation within the "01_Simulations/" folder, respectively.

The folder "00_Base_Files/" contained a set of input files that were needed to execute all simulations. The contents of this folder were copied into each unique simulation folder created within "01_Simulations/" prior to the initiation of that particular simulation.

Two subfolders were within "00_Base_Files/": "00_MATLAB_Files/", which contained all of the MATLAB functions required to run the model, and "01_Model_Iterations/", which contained a folder for the initial model iteration ("001_Iteration/") that has k-files corresponding

to the initial model configuration and simulation. K-files were required for each individual simulation to run in LS-Dyna. They contain information regarding nodal positions, elements, boundary conditions, and prescribed growth parameters as well as the specific data to output from the simulation. Within "00_MATLAB_Files/", a main function "a_Skull_Model_Analysis.m" acted as the parent file for controlling the simulation. The computational growth model was run within this main file by calling additional custom functions within "00_MATLAB_Files/" that allowed the model to progress through the iterative growth process.

The folder "01_Simulations/" contained folders corresponding to each growth simulation. Folders were named based on the specific combination of input parameters implemented for the simulation. For example, with five defined parameters and three levels for each parameter, there was a total of 3^5 =243 unique simulations. Each folder was identified by the unique combination of input parameters at their specific levels, with a name of "X₁X₂X₃X₄X₅_Sim/", where X_i is equivalent to 1, 2, or 3 corresponding to the specific level (low = 1, middle = 2, high = 3) for parameter *i*. Within each unique simulation folder were the subfolders "00_MATLAB_Files/" and "01_Model_Iterations/", as previously stated. For each iteration of the simulation, a new folder "n_Iteration/" was generated, where *n* corresponds to the specific three-digit iteration number of the simulation (e.g., 001, 025, 139). The k-files defining the new configuration of the model were generated within the new iteration folder prior to initiation of that iteration's growth simulation, and all data produced from the simulation were output to the corresponding iteration folder.

9.4.3. Initial Model Setup

Modification of Input Files

The initial section of the computational growth model established the predefined parameters and variables needed to configure the simulation to run with the desired specifications. The section first saved the relevant file paths for the model information and read the k-files corresponding to the initial model configuration. After doing this, it updated the files so that they reflected the specific user-defined modulus values for materials as well as the unique combination of input parameters corresponding to the specific simulation.

Establishment of Element and Node Variables

Once the k-files were updated, variables were established for each element and node in the model to store relevant information related to the model configuration throughout the iterative growth process. The variables were organized as an *n*-by-1 cell array, where *n* corresponds to the number of nodes and elements in the model for the respective node and element cell arrays. Within each individual node and element cell, there was a corresponding structure array that contained fields with both model setup information that was extracted from the k-files and model growth information that was added for each iteration in the growth process.

For each node cell array, the primary structural fields corresponding to the model configuration included the unique node ID number of the node within LS-Dyna, whether the node was on the inner or outer surface of the model, the node ID and cell index number of the "mate node" which was the adjoining node on the outer or inner surface of the element through the thickness, if the specific node was on the inner or outer surface of the model, respectively, and the

specific elements in the model that the node belonged to. There were several node cell structural fields that were updated throughout the growth process. These included the global nodal coordinates $(x \ y \ z)$, the vector from the inner to the outer surface of the model through the thickness of the element between the node and its corresponding mate node $[r_x \ r_y \ r_z]$, the model thickness at the node and mate pair (the magnitude of $[r_x \ r_y \ r_z]$), the unit vector along the node and mate pair $[n_i \ n_j \ n_k]$, the movement of the node from the prior iteration $[dx \ dy \ dz]$, and the strain and stress of the node which was determined by averaging the strains and stresses of all member elements.

For the element cell structural array, the primary fields corresponding to the configuration of the model included the unique element ID number of the element within LS-Dyna, the specific skull component (bone, fontanelle, or suture) that the element corresponded to (bones include frontal, parietal, occipital, and base; sutures include metopic, coronal, sagittal, lambdoid, squamous; and fontanelles include anterior, posterior, sphenoid, and mastoid), the IDs of the nodes making up the element within LS-Dyna and their respective indices in the MATLAB cell array, and the specific nodes corresponding to the inner and outer surfaces of the element. The element cell structural fields that were updated throughout the growth process included element thickness (determined as the average of the thicknesses of each node and mate pair of the element), elastic modulus, strain, and stress.

Post Simulation File Processing

After the simulation was run, the results were output as ELOUT, NODOUT, and ABSTAT files within the run folder. Each of these text-based files contained specific information related to the model configuration at the conclusion of the simulation. Specifically, ELOUT files output the stress and strain state of all elements in the model at the conclusion of the simulation, NODOUT files output the nodal displacements of each node in the model from the simulation, and ABSTAT files contained information regarding the final volume of the interior of the skull model. The ELOUT and NODOUT files were read into MATLAB and processed on an element-by-element and node-by-node basis, respectively. Additionally, the final skull model volume, used to compare the intended volume change for the simulation to the actual volume change to determine the appropriate scale factor, was extracted from the ABSTAT file in MATLAB. To update the model for the subsequent iteration of the simulation, the element strains and nodal displacements were used. Strains were output as global strain tensors and nodal displacements were output as offsets from the initial nodal coordinates using the global coordinate system. The other parameters extracted from the simulation were stored for analysis at the conclusion of all iterations as needed.

APPENDIX E: APPLYING MATERIAL AND THICKNESS GROWTH UPDATES TO THE PEDIATRIC SKULL MODEL

The simulation and analysis processes results in quantification of specific update proportions for all elements and node pair thicknesses in the model. These proportions must be implemented into the next iteration of the model. The process to implement these updates is described in this section.

Updating Element Modulus and Node Pair Thickness

Material updates involve modifying the elastic modulus of an element, while geometric updates involve adjusting the thicknesses of node pairs in the model between its inner and outer surfaces. Material updates for elements in the model are applied by simply updating their elastic moduli for the next growth iteration to reflect the determined material update proportion. To apply geometric updates of node thickness pairs, the node pairs in the model must be modified to reflect the determined thickness update proportion.

While material updates are easy to apply, geometric updates of node thickness pairs are not as straightforward. Not only does the node thickness have to be updated by expanding node pairs differently according to their orientations within the model, but the LS-Dyna simulation process also causes nodal thicknesses to vary from their original values due to deformation of model elements in response to the applied volume expansion. To account for this, the post-simulation configuration of the model node thickness pairs must be adjusted for each growth iteration so that geometric updates can be applied appropriately towards updating node thicknesses prior to the subsequent iteration. This process is described in greater detail in the remainder of this section.

After determining the thickness to apply to a given node pair in the model as described in the previous section, this thickness must be assigned to the node pair by altering the model after the growth simulation. This is because the growth simulation in LS-Dyna alters the original positions and corresponding thickness of the node pair with expansion. Typically, simulations tend to cause compression of the skull model elements due to outward pressure applied to the model through the growth process, altering the corresponding node pair thicknesses. To maintain the post-simulation node pair thicknesses of the model as close to the original thicknesses as possible while simultaneously reflecting the growth that occurred as part of the simulation, the nodal coordinates of the inner surface of the skull model are assigned their updated coordinates based on the growth that occurred from the simulation. To adjust the updated node pair thickness to its new value determined from the update process, the outer surface nodal coordinates are adjusted in a direction along the vector from the inner surface node to its corresponding outer surface node so that the distance between the two represents the intended thickness of that specific node pair. This is described below with specific reference to model simulation outputs and corresponding variable updates.

To update the model after each simulation iteration, a specific process is followed. First, the displacements of all nodes in the model are read from the simulation NODOUT file to determine the post-simulation coordinates of all nodes in the model. Then, unit vectors are calculated for all node pairs in the model from the inner surface node to its corresponding outer

surface node as $[n_i n_j n_k]$. Next, the inner surface coordinates are saved as the new coordinates for the subsequent iteration $(x \ y \ z)$. To determine the new position for the outer surface node, the position of the inner surface is added to the product of the required node pair thickness and the post-simulation unit vector from the inner surface to the outer surface of the model to establish the proper nodal thickness in the direction of simulated growth. Finally, the displacements of each node in the model are determined between their pre- and post-simulation states as $[dx \ dy \ dz]$ and the displacement vector from the inner surface of the model to the outer surface of the model, which has a magnitude of the node pair thickness, is recalculated as $[r_x \ r_y \ r_z]$. This nodal thickness update process is shown schematically in Figure A-2 below. Adjusting the node positions to ensure that the node pairs have the proper positions and thicknesses ensures that the model appropriately reflects the geometric updates required for the subsequent growth simulation.



Figure A-2: Schematic showing the update process for the thickness of a node pair, represented as black connected dots, during a growth iteration. The outer node position updated between the post simulation and final states to possess the proper thickness corresponding to geometric growth magnitude. Parameter calculations are shown as colored arrows.

Base Coordinate Update Methodology

An issue that arose with the growth simulations that needed to be addressed during the model update process was that the portion of the model corresponding to the lower base tended to grow non-physiologically by bulging at contour edges and expanding unnaturally. The result of this, in addition to not representing the true growth pattern of the skull, was that the additional expansion in this region impacted the growth of other areas of the skull because growth occurred through expansion by a predetermined volume. Additionally, expansion of these areas of the base also tended to distort elements after several simulation iterations which ultimately led to convergence problems in later growth iterations. Since the exact configuration of the lower base region was not essential for understanding model growth, and only a general understanding of the

shape of the region was sufficient, a method was required to scale the growth to ensure that there were no convergence errors for simulations. To address this, the base component of the model was treated with a proportional update strategy. This strategy, which is described in the remainder of this subsection, updates the base component nodes based on their offset from the edge of the part.

From the initial configuration of the model, each node belonging to the base component of the model is assigned a value corresponding to its number of nodes offset from the edge of the part. Specifically, up to 12 nodes offset from the edge of the model were considered. Based on the resolution of the model, 12 nodes sufficiently reached the portion of the model which had demonstrated growth problems and associated element distortions which led to convergence problems in simulations. After determining the number of nodes offset from the edge for each base component node, each offset number was assigned a proportion, with a value of 1 corresponding to the edge nodes, a value of 0.1 assigned to all nodes 12 and greater offset from the edge and 12 offset. These intermediate values were determined using a uniform logistic decay curve between 1 and 0.1 to ensure smooth transitions between node pairs which allowed for improved performance in simulations.

After determining node offsets from the model edge and assigning associated update proportions, the proportional growth process was implemented by updating the post-simulation node coordinates from their values determined for the specific iteration as described in the previous section. The original node displacements for all nodes in the base component [dx dy dz] were updated by multiplying them by their associated update proportion, so that nodes at the edge of the model were unaffected and nodes with the maximum offset from the edge of the model were displaced by 10% of their original post-simulation amounts. After this, updated unit vectors were calculated between the inner and outer surface node pairs for all base component nodes. To update the thickness to reflect the scaled growth magnitude, the post-simulation thickness for the current iteration was scaled by the update proportion as well, so that the thickness of the edge node pairs remained the same and the updated thickness of the interior was only varied by 10% of its original change prior to being updated. Finally, similar to the node coordinate update process for the rest of the model described above, the outer surface nodal coordinates were recalculated by adding the position of the inner surface node to the product of the updated node pair thickness and the updated unit vector from the inner surface node to the outer surface node of the model, and the displacements of each node in the model between pre- and post- simulation states [dx dy dz] and the displacement vector ($[r_x r_y r_z]$ with a magnitude of the node pair thickness) were recalculated to reflect the scaled growth.

While not necessarily having a true physiological basis in its methodology, this scaled update methodology for the base component of the model ensures that the simulations run properly to completion for each growth iteration and that the configuration of the base component of the model exhibits an appropriate morphology as compared to the developing pediatric skull.

Ensuring Symmetric Model Growth

Another issue that arose from simulations in addition to the non-physiological growth of the base component was that the model exhibited a non-symmetric growth pattern over the course of multiple simulation iterations, resulting in a skewed configuration of the final model. Since the model should ideally exhibit a symmetrical growth pattern about its centerline due to a uniform expansion process, this was an abnormality that was corrected as part of each model iteration, ensuring a symmetric growth pattern for the model. This symmetric growth update is described in the remainder of this subsection.

Initially, each node and element are assigned a reflected mate corresponding to the node or element in the same position on the opposite side of the sagittal plane of the model. This is possible because the initial configuration of the model is symmetric about its sagittal plane, which passes through the model centerline, dividing it into left and right halves that are mirror images of each other.

After each node and element are associated with reflected mate nodes and elements, the growth of the model is made symmetric, specifically in terms of the modulus and the configuration of the model. To update the elements in the model, the modulus of each element and its corresponding reflected mate are averaged, and this updated average element modulus is assigned to each of the elements.

To update the node positions in the model, the positions of each node and its corresponding reflected mate are averaged, preserving the original sign of the y-coordinate, since the sagittal plane of the model is the y = 0 plane. This average coordinate location is then assigned to each of the nodes. Additionally, the growth direction [dx dy dz], through-thickness vector $[r_x r_y r_z]$, thickness, and through-thickness unit vector $[n_i n_j n_k]$ are updated using these updated coordinate locations. For all elements symmetric about the sagittal plane, the modulus is kept at its previously determined value. For all nodes lying on the sagittal plane of the model, the growth magnitude for the specific iteration is determined as the magnitude of the [dx dy dz] vector. In addition, a unit vector containing the x and z components of the growth, which are the growth components occurring within the sagittal plane, is determined. Finally, the original growth magnitude is multiplied by this sagittal plane-growth unit vector and this corresponding position update is applied to each node falling within the model sagittal plane, preserving the growth magnitude of the sagittal plane nodes in the model while simultaneously ensuring growth occurs symmetrically within the plane.

By updating nodes and elements with reflected mates across the sagittal plane of the model to have averaged respective coordinates and modulus values and by ensuring that nodes within the sagittal plane of the model have growth occurring within that plane, model growth stays symmetric throughout each growth iteration. Symmetric growth simultaneously ensures that the growth process acts physiologically over repeated growth iterations.