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ORIGINAL PAPER

Computational neurotrauma—design, simulation, and analysis of controlled cortical impact model

Haojie Mao · King H. Yang · Albert I. King · Kai Yang

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Abstract The controlled cortical impact (CCI) model is widely used in many laboratories to study traumatic brain injury (TBI). Although external impact parameters during CCI tests could be clearly defined, little is known about the internal tissue-level mechanical responses of the rat brain. Furthermore, the external impact parameters tend to vary considerably among different labs making the comparison of research findings difficult if not impossible. In this study, a design of computer experiments was performed with typical external impact parameters commonly found in the literature. An anatomically detailed finite element (FE) rat brain model was used to simulate the CCI experiments to correlate external mechanical parameters (impact depth, impact velocity, impactor shape, impactor size, and craniotomy pattern) with rat brain internal responses, as predicted by the FE model. Systematic analysis of the results revealed that impact depth was the leading factor affecting the predicted brain internal responses. Interestingly, impactor shape ranked as the second most important factor, surpassing impactor diameter and velocity which were commonly reported in the literature as indicators of injury severity along with impact depth. The differences in whole brain response due to a unilateral or a bilateral craniotomy were small, but those of regional intracranial tissue stretches were large. The interaction effects of any two external parameters were not significant. This study demonstrates the potential of using numerical FE modeling to engineer better experimental TBI models in the future.

H. Mao (✉) · K. H. Yang · A. I. King
Bioengineering Center, Wayne State University, Detroit, MI 48201, USA
e-mail: hmao@wayne.edu

K. Yang
Department of Industrial and Manufacturing Engineering, Wayne State University, Detroit, MI 48201, USA

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1 Introduction

Traumatic brain injury (TBI) continues to be a serious societal problem that affects more than 1.4 million Americans each year (National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, http://www.cdc.gov/injury, 2006). In the European Union, brain injury accounts for one million hospital admissions per year (Mauritz et al. 2008). Fatality due to TBI can occur in children and adults during their most productive years, and the associated societal and economic costs are enormous. Direct medical cost and indirect costs such as lost productivity of TBI totaled an estimated $60 billion in the Unites States in 2000 (Finkelstein et al. 2006). Additionally, there are many survivors with severe brain damage and many more with moderate or mild impairment, who require continuous medical attention (Krause et al. 1996; Fearnside and Simpson 1997; Graham and Gennarelli 1997; Goldstein and Levin 2001; Goldstein et al. 2001; Hoffmann et al. 2002; von Wild and Wenzlaff 2005).

Disabilities resulting from TBI depend on several factors, such as location and severity of injury. A significant shortcoming in correlating real world injuries with predictions from a validated finite element (FE) model in order to establish injury threshold lies in the fact that input parameters in real world TBI's are not well controlled, and the location and extent of injury cannot be documented in sufficient detail. The controlled cortical impact (CCI) rat model is one of the most frequently used animal models because the location and magnitude of mechanical input are readily controllable and quantifiable. TBI's resulting from CCI have been used

in a wide range of studies to investigate injurious effects, including problems with cognition (thinking, memory, and reasoning), sensory processing (sight, hearing, touch, taste, and smell), communication (expression and understanding), and behavior or mental health (depression, anxiety, personality changes, aggression, acting out, and social inappropriateness) (Vink and Mcintosh 1990; Laurer and Mcintosh 1999; Finnie and Blumbergs 2002; Ommaya et al. 2002). Additionally, this experimental model is mechanically simple because it imposes little or no angular acceleration on the skull and hence fewer variations in mechanical input. Nevertheless, the different experimental parameters (impact depth, impact velocity, impactor size, impactor shape, craniotomy pattern, etc.) that are employed by various researchers render the model rather complex, making it nearly impossible to compare results generated by the various laboratories. Other than impact depth and velocity, which were believed to determine injury severity, impactor size, impactor shape, also the number of craniotomies can contribute to variances observed in post-impact tissues. Furthermore, the combined effect of these external parameters in CCI remains largely unknown. For example, compare a CCI with high impact depth and low velocity to one with a low impact depth and high velocity cannot be handled in a straightforward manner. Therefore, it is crucial to systematically analyze the effect of external parameters based on the global intracranial tissue responses.

Data in literature supports the premise that brain tissue injury was the direct result of mechanical insult which can be modeled numerically to relate brain injury to intracranial response (e.g. Bain and Meaney 1999; Morrison et al. 2003; Cater et al. 2006; Morrison et al. 2006; Laplaca et al. 2007). Therefore, the primary injury caused by CCI-induced tissue strains could be numerically simulated using a computational brain model. For this study, we will use the validated 3D FE rat brain model developed by Mao et al. (2006). This model simulates all essential anatomical features of a rat brain, including the cortex, hippocampus, thalamus, hypothalamus, corpus callosum, brainstem (midbrain, pons, and medulla oblongata), cerebellum, lateral ventricle, 3rd and 4th ventricle, internal capsule, external capsule, olfactory bulb, and part of the spinal cord based on a rat brain atlas (Paxinos and Watson 2005). The model consists of 255,700 hexahedral elements with a typical spatial resolution of 200 microns. About 85% of elements have an edge length between 100 and 200 μm, 10% of elements have an edge length of between 200 and 300 μm, 5% of elements have an edge length of less than 100 μm, and the minimal edge length is 44 μm. Because reduced integration scheme was used in explicit finite element simulations, strain magnitude was only calculated at the center of each element. For this reason, discrepancies in strain might exist between the edge and center of the element. Nonetheless, such discrepancies are likely very small because of the small element size. For convergence study, it was reported by Mao et al. (2010) that the current FE rat brain model with a typical spatial resolution of 200 μm converges sufficiently. Less than 0.5% of all solid elements in the model have a warpage of greater than 45 degrees. In the study reported by Mao et al. (2006), the FE model was numerically stable when simulating large direct intrusion into brain tissues. At the time of the maximal tissue deformation, no excessive distortions were observed, and all simulations ran uninterrupted for the entire intended duration. Thus, the model was deemed suitable for the current study. For injury measurement, Takhounts et al. (2003, 2008) proposed the use of a cumulative strain damage measure (CSDM) to calculate the total volume of the brain that exceeded a preset injury threshold. In our previous study, it was reported that the maximum principal strain (MPS) above 0.30 could predict contusion volume observed in CCI model (Sutton et al. 1993; Kochanek et al. 1995; Scheff et al. 1997; Chen et al. 2003). Furthermore, a linear relationship correlating tissue MPS response to the percentage of cell loss was found (Mao 2009). A new measure to predict TBI severity, cumulative strain damage percentage measure (CSDPM), was proposed (Mao 2009). The effect of external impact parameters on injury outcome could be studied by calculating contusion volumes (CSDM 0.30) and CSDPM scores for different CCI settings.

In this study, a series of CCIs with scenarios never explored in previous experimental models will be simulated to further evaluate the potential benefit of applying a FE model to design animal experimental studies without the need to undergo many trials and errors. The effects of external parameters on injury outcome will be systematically studied.

2 Methods

2.1 Review of external CCI impact parameters in the literature

Before utilizing the computational model to predict CCI-induced injuries, the PubMed database was searched to identify the most used CCI experimental settings for the adult rat model. A total of 235 papers were found and categorized according to the mechanical parameters utilized (review manuscript being prepared separately). Among these papers, 122 papers reported the use of a unilateral (single) craniotomy, 17 papers reported bilateral craniotomy use, while 95 papers did not report this information. In one unique study, both unilateral and contralateral craniotomies were studied (Meaney et al. 1994). Among the 222 papers in which the impact depth was reported, 12 papers utilized two depth levels and six reported three depth levels. The most common impact depths used were 2.0 mm ($n = 77$), 2.5 mm ($n = 52$),

and 3 mm ($n = 29$). Of the 219 studies in which the impact velocity was reported, the top three most used impact velocities were 4 m/s ($n = 75$), 7 m/s ($n = 29$), and 6 m/s ($n = 26$). There were two studies employing two velocity levels and four studies employing three velocity levels. The impactor diameter used in these studies varied largely from 2 to 9.5 mm while a majority of the studies employed a 5 mm ($n = 75$) or a 6 mm ($n = 39$) diameter impactor. The contact time, or hold time after the impactor reached its peak compression, ranged from 20 to 500 ms. The top three contact times used were 50 ms ($n = 22$), 150 ms ($n = 13$), and 300 ms ($n = 14$). A handful of studies in which the shape of the cylindrical impactor shape was reported, it was mostly flat or convex in shape.

2.2 Design of computer experiments (DOCE)

Design of Experiments (DOE) has been widely used to study multiple variables simultaneously, in many fields such as biological, agricultural, and automotive engineering (e.g. Roy 2001; Antony 2003). Recently, the same concept has been extended to computational simulations to study the effect of different factors. Based on the literature review described above, the most used impact parameters could be readily identified. The typical CCI experiment would involve the use of an impact depth of 2 mm (e.g. Sutton et al. 1993), an impact velocity 4 m/s (e.g. Chen et al. 2003), an impactor diameter of 5 mm (e.g. Scheff et al. 1997), and a unilateral craniotomy (e.g. Kochanek et al. 1995). To vary the impact parameters, they could be increased by 50% over the baseline level. For example, the impactor area would be increased by about 50% by increasing the impactor diameter from 5 to 6 mm, in the second level of DOE. Although the flat impactor was used in most of the studies reported in the literature, our preliminary FE simulations demonstrated that the shape of impactor affected the intracranial responses during CCI. The flat-shaped impactor will be defined as the baseline shape and the spherical impactor as the second level. Based on the above review, a five-factor two-level factional factorial analysis was designed to systematically analyze the effect of impact parameters (Table 1) without any preliminary screening. The five external parameters were impact depth, impact velocity, impactor shape, impactor diameter, and craniotomy pattern. Using a total of 16 cases, DOE design reached resolution V in which the main effects and two-factor interactions could be evaluated independently. The CSDM injury predictor proposed by Takhounts et al. (2003, 2008) was calculated using a MPS threshold of 0.30 (Eq. 1). Additionally, the new CSDPM (Eq. 2) based on the relationship between the neuronal injury percentage and MPS proposed (Mao 2009) were analyzed. DOE and analysis were performed using Minitab (Ver. 15.0, State College, PA).

Table 1 Factional factorial design of computational CCI experiments

Case no.	Impactor		Craniotomy	Impact	
	Diameter (mm)	Shape		Depth (mm)	Velocity (m/s)
1	5	Sphere	Bilateral	3	4
2	6	Sphere	Unilateral	2	6
3	6	Sphere	Bilateral	3	6
4	6	Sphere	Unilateral	3	4
5	6	Sphere	Bilateral	2	4
6	6	Flat	Bilateral	3	4
7	5	Sphere	Bilateral	2	6
8	5	Flat	Unilateral	2	6
9	5	Flat	Bilateral	2	4
10	6	Flat	Unilateral	2	4
11	5	Flat	Bilateral	3	6
12	6	Flat	Unilateral	3	6
13	6	Flat	Bilateral	2	6
14	5	Flat	Unilateral	3	4
15	5	Sphere	Unilateral	3	6
16	5	Sphere	Unilateral	2	4

$$\text{CSDM} = \sum \text{volume of element experiencing MPS above 0.30} \quad (1)$$

$$\text{CSDPM} = \sum_{i=1}^{N} \text{neuronal loss percentage per MPS} * [\text{volume ratio } (i)];$$

$$\text{Neuronal loss percentage per MPS} = 1.992 * \text{MPS} - 0.028$$

$$\text{Volume ratio (i)} = \frac{\text{volume of element (i)}}{\text{total brain volume}} \quad (2)$$

i represents the element number, and N is the total number of elements in the FE model.

Using the same 16 impact scenarios selected for DOCE, two additional groups representing small fluctuations in the size of the brain or in the white matter material properties were studied. The first group represents a fully mature rat brain when compared to the average size rat used. Paxinos and Watson (2005) reported that there is an average increase of 7% in mature rat head. A new FE model representing this large size rat was developed by a uniform increase of 7% along the x-, y-, and z-direction from the model developed by Mao et al. (2006). In the second group, a stiffer white matter was simulated by increasing the short- and long-term shear moduli to 2.15 and 0.64 kPa, respectively. The selection of a stiffer white matter was based on the study by Arbogast and Margulies (1997) in which the porcine white and gray matters were compared.

Table 2 FE model-predicted responses for 16 DOCE cases

Case no.	CSDM_0.30 (mm^3)	CSDM_0.25 (mm^3)	CSDM_0.35 (mm^3)	CSDPM (%)
1	76.76	137.83	42.67	15.53
2	69.13	118.51	34.31	15.37
3	199.29	299.85	120.59	24.35
4	113.73	191.47	67.60	19.03
5	40.23	91.97	15.50	14.34
6	269.38	384.74	182.94	28.05
7	67.88	123.15	32.98	15.97
8	79.40	128.72	46.31	16.08
9	65.15	123.49	33.50	16.01
10	83.64	142.05	36.91	16.96
11	214.24	309.34	143.58	24.67
12	412.84	555.90	311.29	34.35
13	116.20	182.17	67.34	19.19
14	146.69	217.02	101.58	20.28
15	91.00	145.73	54.05	16.75
16	27.87	64.23	12.84	10.61

2.3 FE simulation and analysis

The computational simulations were performed using LS-DYNA 970 (LSTC, Livermore, CA). For efficiency purposes, CCI injury was simulated for only the first 2 ms of impact during which the peak of MPS would have been reached. MPS values were tabulated at 0.1 ms intervals for all brain elements. After all the simulations were completed, an in-house program developed by the author using C++ (Microsoft, Seattle, WA) was used to calculate the peak MPS each element experienced during CCI. Then the total volume of the elements experiencing a MPS of above 0.30 during the CCI impact (CSDM 0.30) was calculated for each case. Furthermore, effect of two different pre-selected CSDM contusion thresholds (0.25 and 0.35) was studied to determine if the ranking of individual and coupled variables altered significantly. The CSDPM score for each case was calculated by applying Eq. 2.

The effects for individual and coupled variables were analyzed using Pareto and main effect charts. In a Pareto chart, the horizontal bar length shows the "absolute value" due to the effect of each individual and coupled variables. For example, bar lengths for individual variable in a Pareto chart predicted by CSDM and CSDPM show the contusion volume in mm^3 and percentage of cell death, respectively. The bar length for "coupled variables" in a Pareto chart shows the interactive effect of two variables. The interaction is a measure of "non-additive effect." Additionally, the magnitude needed to have statistical significant effect is also indicted on a Pareto chart based on the Lenth's method (Lenth 1989). In physical experiments with a combined set of variables, multiple data points (replicates) are generated even under identical experimental conditions due to the effect of "noise." In contrast, "computer experiments" yields only one data point (single replicate). The Lenth method based on a t-distribution is specially designed to study the effect of computer experiments by assuming only small portions of variables are significant. The main effect chart further depicts the mean differences of FE model-predicted injury measures due to each individual variable.

3 Results

The CSDM-predicted contusion volumes and CSDPM-predicted percentage of cell death for all 16 cases are listed in Table 2. Contusion volumes estimated using MPS threshold values 0.25 and 0.35 are also included (Table 2). Factorial analysis, in the form of a Pareto chart (Fig. 1), indicates that impact depth and impactor shape affect the CSDM-predicted contusion volume in a statistically significant manner. For average rat brain model, increasing the impact depth from 2 to 3 mm increased the mean FE model-predicted contusion volume from 68.7 to 190.5 mm^3 (Fig. 2). On the other hand, the mean FE model-predicted contusion volume decreased from 173.4 to 85.7 mm^3 when a flat impactor was changed to a spherical one. Furthermore, the flat impactor tended to induce high MPS along the impactor rim while the MPS produced by the spherical impactor distributed along radial direction (Fig. 3, Cases 14 and 15). The next variable is impactor

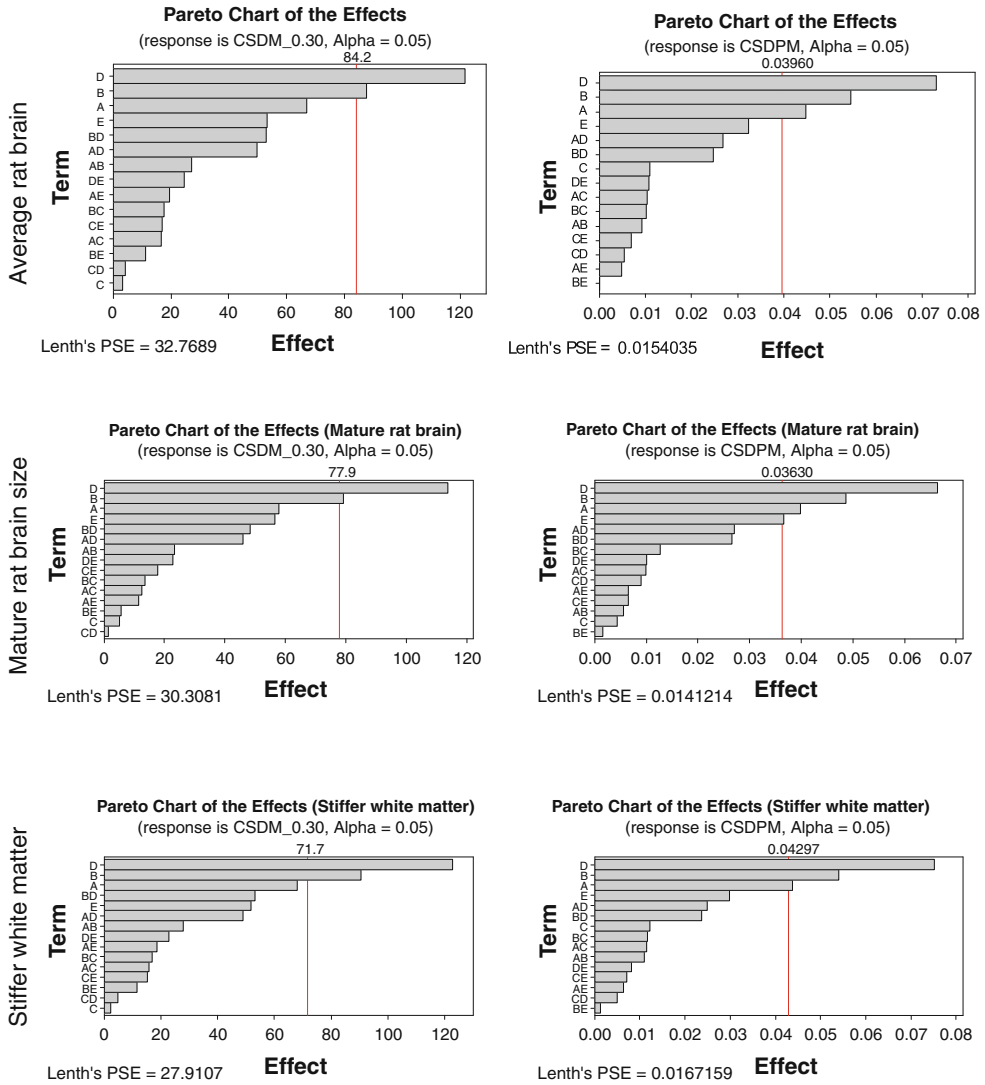


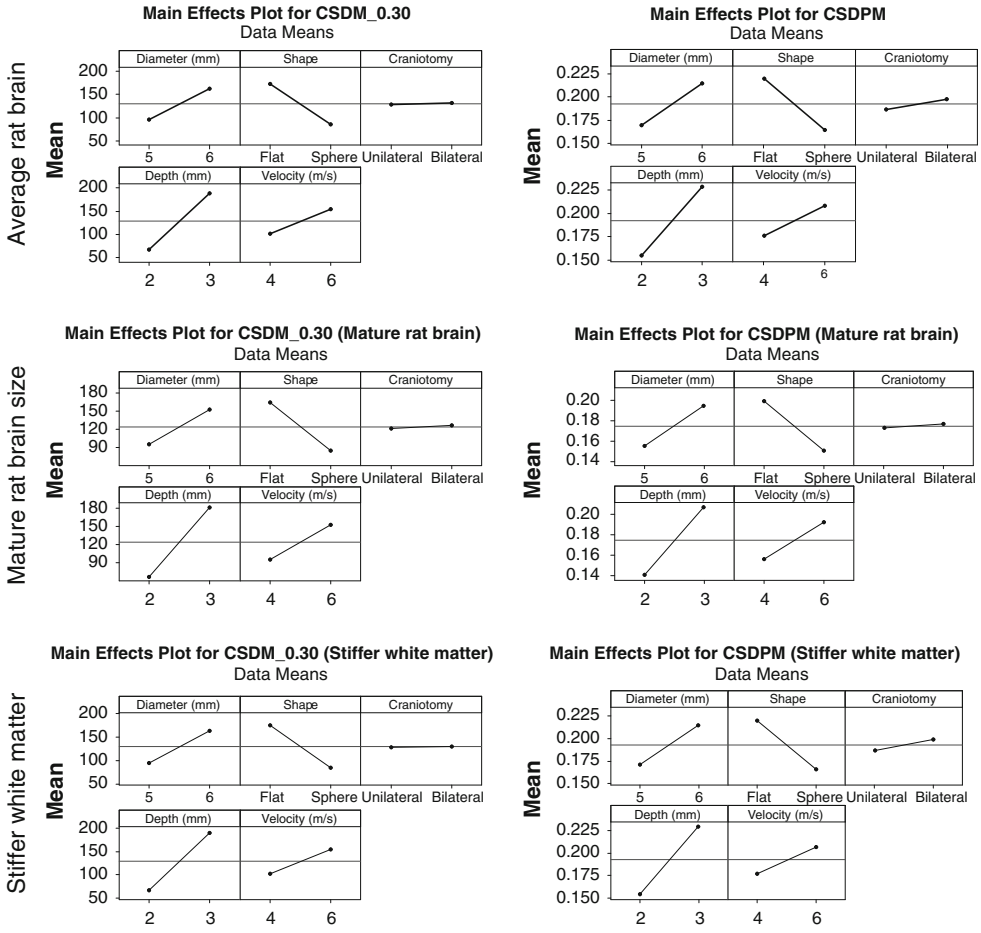
Fig. 1 Pareto analysis for the average rat brain (*top row*), mature rat brain (*middle row*), and stiffer white matter (*bottom row*) cases. **a** impactor diameter, **b** impactor shape, **c** craniotomy pattern, **d** impact depth, **e** impact velocity

diameter which also significantly affects CSDPM but not as significantly as impact depth and impactor shape. The mean percentage of FE model-predicted cell death increased from 15.6 to 22.9% when the impact depth was increased from 2 to 3 mm, from 22.0 to 16.5% when a flat impactor was replaced by a sphere one, and from 17.0 to 21.5% when the impactor diameter was increased from 5 to 6 mm. Only small variations were found due to variations in the size and material properties on CSDM or CSDPM-predicted injury outcomes (Fig. 2).

Factorial analysis showed little overall effect on CSDM-predicted mean contusion volume and CSDPM-predicted mean percentage of cell death when comparing unilateral and bilateral craniotomy cases (Fig. 2). However, a coronal view of the rat brain at the center of the impactor shows very different MPS contours when Cases 11 and 14 are compared (Fig. 3). It can be seen that a bilateral craniotomy induced higher MPS to the contralateral site where a second craniotomy was simulated. It is believed that a properly designed second craniotomy can guide brain tissue deformation in a CCI animal model to target a specific region of interest.

Following impact depth, impactor shape, and impactor diameter, impact velocity only ranked as the fourth most important factor affecting CSDM and CSDPM. The combination of depth and diameter or shape ranked as the fifth and sixth important factors for calculated injury output, respectively. Since depth, shape, and diameter are already the three leading factors affecting injuries, they are most critical when designing appropriate injury models.

Figure 4 shows the elements which experienced a MPS above 0.30 for all 16 cases. Generally, the high strain elements were near the impact site and distributed deep into the



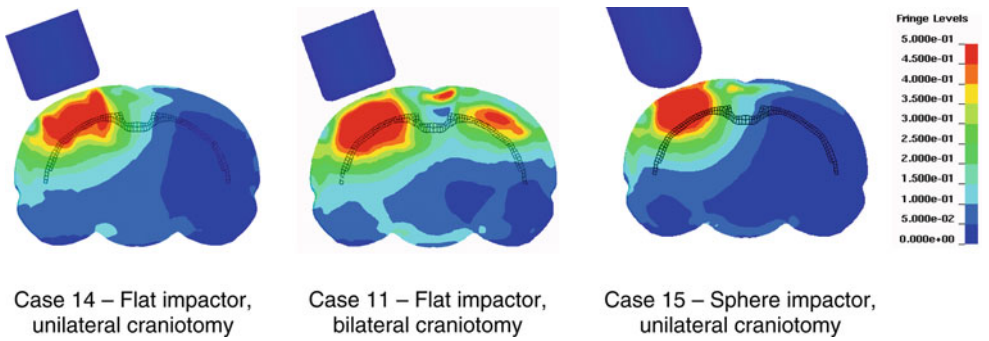


Fig. 2 Main effects of external CCI parameters on CSDM-predicted contusion volume in mm^3 and CSDPM-predicted fraction of cell death. The average rat brain, mature rat brain, and stiffer white matter were listed in the *top row, middle row*, and *bottom row*, respectively

Fig. 3 MPS induced in the contralateral site by using bilateral craniotomy (Case 11) and sphere impactor (Case 15)

brain starting from the surface. More injuries in the contralateral hemisphere could be induced when using a bilateral craniotomy (for example, Cases 3, 6, and 11). Furthermore, the distribution of injured elements in the contralateral site was generally more focal compared to the injury in the ipsilateral site (for example, Case 3) and seemed to be constrained to the region underneath the contralateral craniotomy. This finding might indicate an important biomechanical basis for designing desired brain trauma by applying multiple craniotomies appropriately.

4 Discussion

The effect of external parameters and of combinations of parameters on intracranial biomechanical responses was systematically analyzed using the validated FE rat brain model. It was found that impact depth and impactor shape are the two leading factors affecting tissue strains. Figure 1 shows that the impactor diameter has a significant effect on the CSDPM but not CSDM. This is probably due to different weighting factors used in these two injury measures.

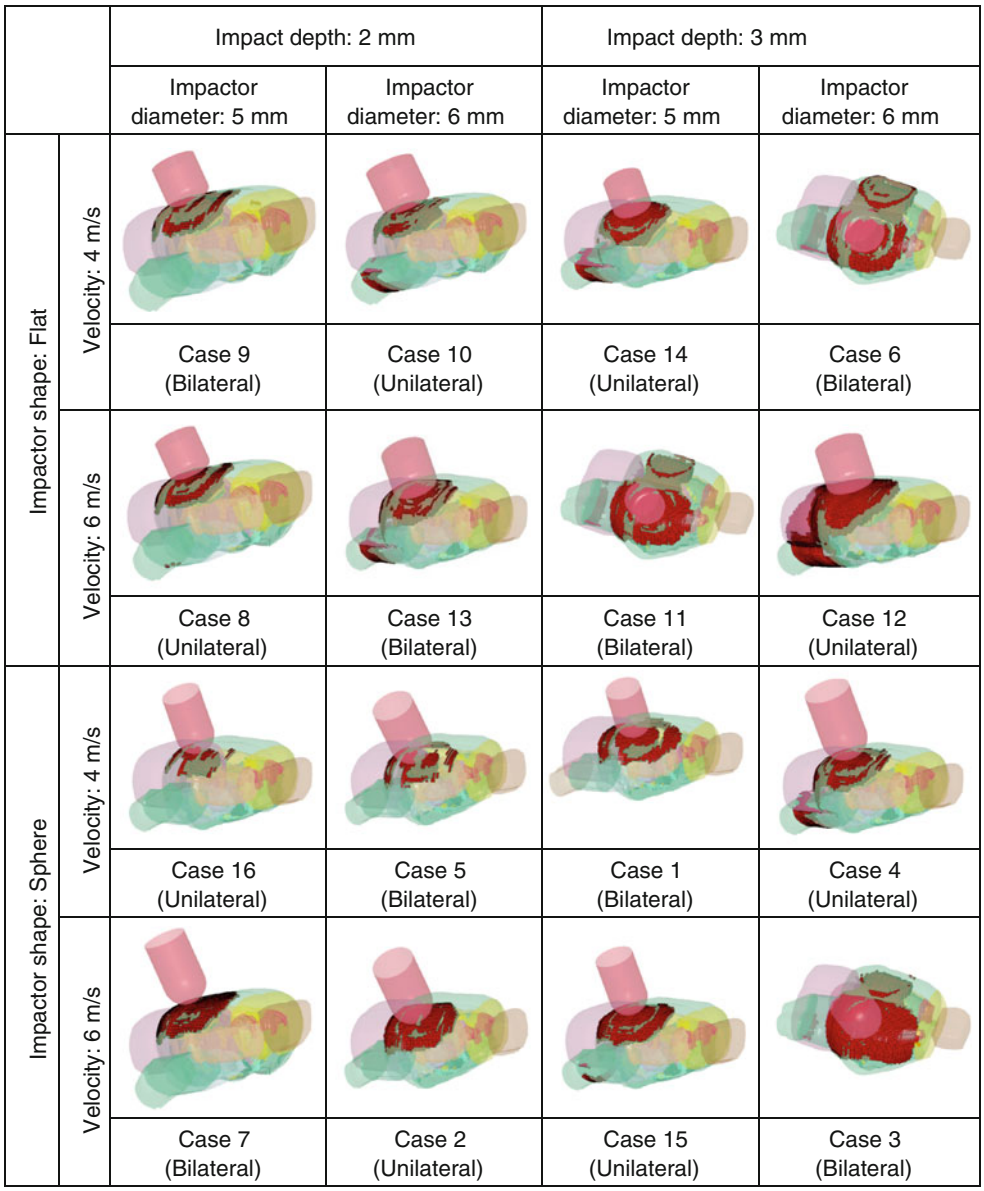


Fig. 4 Elements experiencing a MPS higher than 0.3 during the CCI were highlighted as *red color* with meshes

In the CSDM, all elements with a peak strain exceeded the pre-determined threshold were treated as having the same effect. On the contrary, the higher the strain value predicted for a particular element, the higher the CSDPM would be. While it is intuitive to expect more injury with a greater velocity and a deeper impact, we need the FE model to tell us that the application of a larger impactor, especially one with a flat surface, can induce more injuries.

The effect of impact velocity was found to be not significant. This is very interesting since a wide range of velocities were used in different labs to induce desired injury levels. The explanation may reside in the experimental technique to control the depth of penetration. Brody et al. (2007) found a significant amount of overshoot in a pneumatically powered CCI impactor at high speed, because the mechanical stopper, made of aluminum, rubber, or steel, was unable to stop the high speed impactor instantly after it reached the preset depth. Furthermore, the overshoot distance tended to increase with speed (Brody et al. 2007). Since most CCI experiments were performed with a pneumatic device, the impact velocity could indeed affect the actual impact depth. During the computational design of experiments, the impact depth was accurately defined and was not affected by the velocity setting. Consequently, the velocity was only the fourth ranking effect for both CSDM and CSDPM.

The visual description of injured elements for all 16 cases showed variations in injury distribution that were larger than expected, for a reasonable range of external

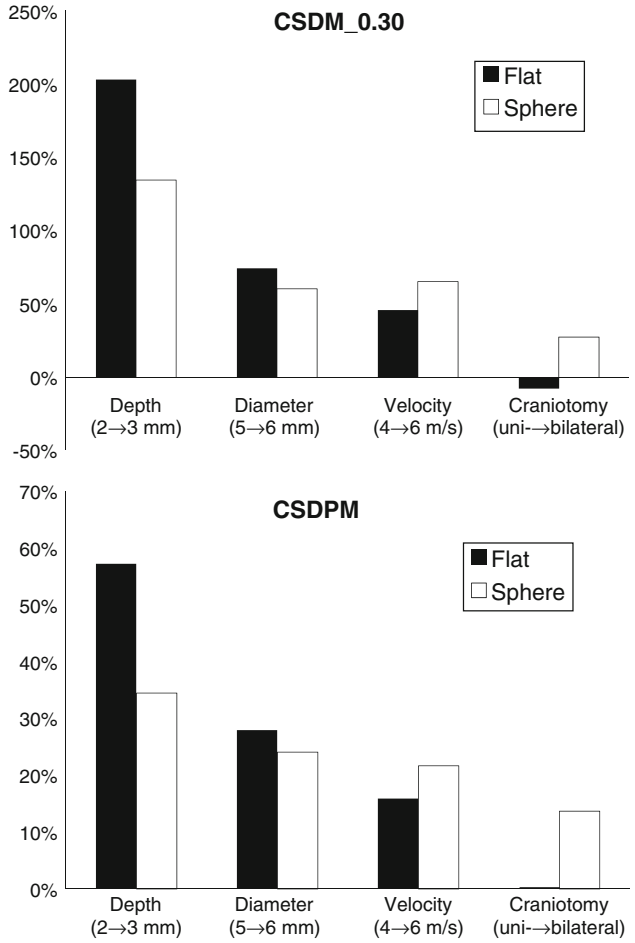


Fig. 5 Percentage changes in FE model-predicted injuries in the average rat brain due to changing the impact depth from 2 to 3 mm, impactor diameter from 5 to 6 mm, impact velocity from 4 to 6 m/s, and pattern of craniotomy from unilateral to bilateral for flat impactor and sphere impactor groups

impact parameters found in the literature. Therefore, without knowing all the external parameters and the corresponding intracranial tissue responses, comparison of CCI results from different labs is very difficult. For example, a simplified description of "2-mm impact depth CCI" could include several totally different tissue strain responses with injury volume varying by as much as four times, as can be seen from Cases 13 and 16.

One interesting finding is related to highly strained elements in the brain stem region, which is generally believed to induce "focal" injuries. A large number of highly strained elements were found in the brainstem region in cases with high impact depth or velocity, mostly using a flat-shaped impactor (for example, Cases 6, 12, 13, and 14). The application of a bilateral craniotomy could greatly reduce the strain in the brainstem region, possibly due the extra opening which allowed brain tissue to move laterally instead of caudally during the impact. However, since injury tolerance of the brainstem remains largely unknown, possible injuries in the brainstem area need to be investigated further.

To depict the effects for the impactor depth, impactor diameter, impact velocity, and site of craniotomy due a flat impactor or a spherical impactor, simulation results from the average rat brain group were further analyzed. The baseline case has an impact depth of 2 mm, impactor diameter of 5 mm, impact velocity of 4 m/s, and unilateral craniotomy. Percent changes from 2 to 3 mm impact depth, 5 to 6 mm impactor diameter, 4 to 6 m/s impact velocity, and unilateral craniotomy to bilateral craniotomies as a result of a flat or spherical impactor are shown in Fig. 5. Effects for increasing the impact depth from 2 to 3 mm and impactor diameter from 5 to 6 mm were higher in the flat impactor group compared to spherical impactor group. On the other hand, effects for increasing the velocity from 4 to 6 m/s and number of craniotomy were higher in the spherical impactor group. The fact that a spherical impactor has more effect when the craniotomy pattern was changed from unilateral to bilateral is very interesting. In the flat impactor group, bilateral craniotomies did not alter the CSDM and CSDPM-predicted injuries by much when compared to the unilateral craniotomy. In contrast, the bilateral craniotomies increased the CSDM by 27.3% and CSDPM by 13.7% in the spherical impactor group (Fig. 5). This is probably due to the geometrical effect

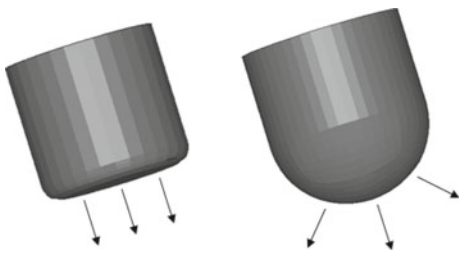


Fig. 6 A schematic view of loading direction for a flat and spherical impactor

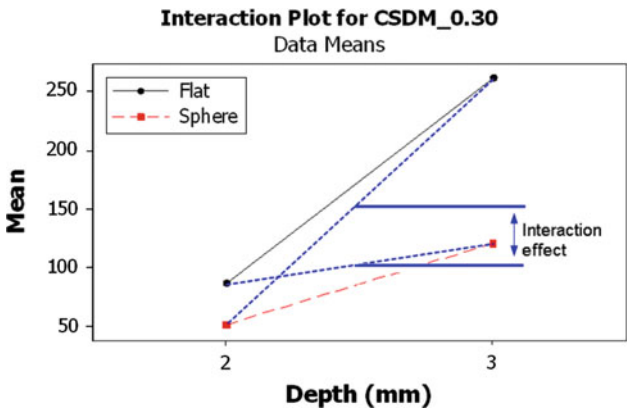


Fig. 7 Interaction effect of FE model-predicted contusion volume due to impactor shape and impact depth and the explanation of interaction effect for these two variables

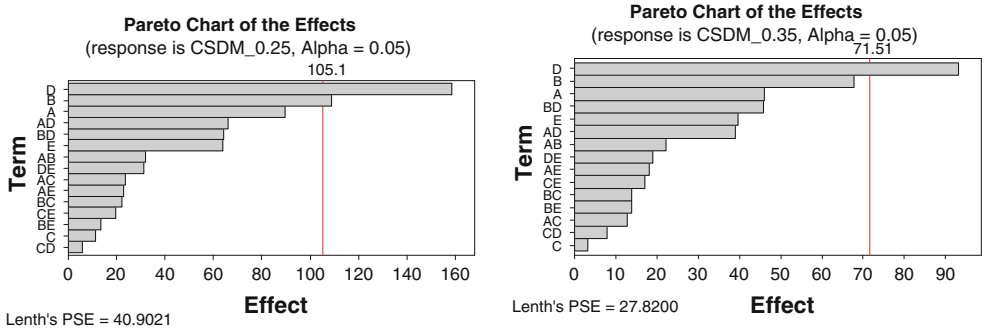


Fig. 8 Effect analysis of changing the MPS threshold to 0.25 and 0.35. **a** impactor diameter, **b** impactor shape, **c** craniotomy pattern, **d** impact depth, **e** impact velocity

by which a spherical impactor can push brain tissue in radial direction while a flat impactor tends to compress brain tissue along impact direction (Fig. 6). Consequently, more injuries were predicted by the spherical impactor in the cases with bilateral craniotomies because it acted to strengthen a lateral movement of brain tissues.

Figure 7 shows the interaction plot for the model-predicted contusion volume due to impact depth and impactor shape. When the impact depth increased from 2 to 3 mm, the CSDM increased 69 mm^3 (from 51 to 120 mm^3) for a spherical impactor and 175 mm^3 (from 86 to 261 mm^3) for a flat impactor. It was also clear that the solid line (flat impactor) and dotted line (spherical impactor) were not parallel. Further, the mid-points for the lines connecting the "flat impactor-3 mm impact depth and spherical impactor-2 mm impact depth" and the "spherical impactor-3 mm impact depth and flat impactor-2 mm impact depth" were at a distance. In DOE terminology, the impactor shape and impact depth do have interaction. More research is needed to separate these two effects.

Figure 8 shows the Pareto charts due to different MPS contusion thresholds selected for predicting the contusion volume. Results indicate that the impact depth, impactor shape, and diameter are still the top three leading factors despite of different MPS thresholds. However, the significant line shifted to the right for the prediction with an injury threshold of 0.35. More studies need to be conducted to determine the precise injury threshold before the FE model is further used in designing new CCI experimental model.

Brain internal tissue strains could offer a biomechanical basis for designing future experimental models to produce a "desired" injury more precisely; that is, with an appropriate contusion core and cell damage level. In addition, a fully validated numerical rat brain model can offer a global internal tissue strain description for comparing experiments performed at different labs, with careful consideration of different functions of various anatomical regions.

5 Conclusion

A systematic computational design of experiments for CCI was performed. Besides impact depth, impactor shape and impactor diameter were found to affect brain internal responses. However, the effect of impact velocity (even with a 50% change) is very limited. The application of a bilateral craniotomy did not affect overall brain responses by very much, but it changed the intracranial strain distribution by shifting some of the high strains more diffusely to the contralateral hemisphere. This numerical rat brain model can be used to computationally design more refined experimental models of neurotrauma and enable researchers to accurately design a site- and severity-specific rodent TBI model while reducing the number of rats needed for any specific study by eliminating the current trial and error method of developing new experimental models.

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