Tissue Strain-Based Scaling of Spinal Cord Injury in Animal Models: From Rat to Cat

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Introduction: Animal contusion models have been developed as surrogates for investigating Spinal Cord Injury (SCI) in humans (Anderson et al., 2005; Sharif-Alhoseini et al., 2017; Galle et al., 2017; Russell et al., 2012). Scaling-up of such animal models is of paramount importance for the development of clinical therapies, while optimizing/minimizing the use of animals in research. Herein, we investigate the ability of tissue strain densities (TSD) as an engineering scaling-up biomarker permissive to develop a cat SCI model, based on data from a rat model, with improved SCI repeatability and accuracy. SCI damage was compared in both animal models using histological analysis of the lesion extent in spinal cord.

Materials and Methods: We conducted both experimental and computational studies to determine TSD values in the SCI rat model following a force-controlled impact. A C4 midline contusion was performed on seven Sprague-Dawley rats (female, 32 weeks old) using a 3.5 mm in diameter spherical impactor (Zareen et al., 2017). One rat and a cat (adult female) were scanned using MRI (7.0 Tesla 70/30 Bruker Biospec, resolution 0.234 mm) and microCT (Siemens Inveon, resolution 0.196 mm). For both animals, MRI and CT images were co-registered and segmented in ScanIP (Simpleware, Exeter, UK) for bone, dura mater, cerebral spinal fluid (CSF), white and gray matter. The segments C2-6 were digitally isolated and a C4 laminectomy was artificially performed for the contusion FE model. Adaptive volumetric meshes of respectively ~0.4 and ~0.6 M tetrahedral elements were generated for the rat and the cat (+Fe module, ScanIP) and imported into Abaqus (Simulia, v6.14-3). In the rat model boundary conditions and the total time (T.t) for the simulation were applied to match the experiment (impactor velocity, 122 mm/s; T.t., 0.135 s). Material properties were initially assigned according to Maikos et al. (2008) and fitted to the experimental reaction force curves using an inverse analysis in Abaqus. The combination of bulk modulus (K), shear modulus (G) and Poisson ratio (ν) resulting into the best fitting was used for the FE analysis of the rat contusion SCI. The tissue strain density level observed in the numerical simulation for the rat were then used to predict the necessary force needed to produce a similar injury in the FE contusion model of the cat. Four different combinations of impactor diameter (3.5 or 5.0mm) and tip shape (flat or spherical bottom) were created in Abaqus and computationally tested.

Results and Discussion: Strain Probability Density (SPD) and Cumulative Distribution Function (CDF) measurements were obtained for the rat contusion model. 90%, 95% and 99% of the cumulative probability was achieved respectively at 0.163, 0.174 and 0.193 strain. With the maximum limit of 0.193, the strain map from the simulation matched the histologic results of the rat lesion with higher strain values close to the lesion area. Based on these findings, the 0.193 strain was adopted as an injury biomarker threshold for the cat simulations as well. The force and the T.t needed for producing the targeted 0.193 strain were found different for each actuator size and tip shape. Specifically, a force of 480, 385, 322 and 262 kDyn were achieved in a T.t of 25.5, 26, 24.5 and 24 ms respectively for the 5mm_flat, 5mm_spherical, 3.5mm_flat and the 3.5mm_spherical actuator. The strain maps produced for each cat model were also slightly different. For the 5mm_flat bottom actuator the lesion extended more into the lateral region of the spine than in other models, while spherical actuators produced a concentrated high strain region underneath the actuator impact at midline.

Conclusions: Tissue strain density is a good quantitative predictor of tissue damage in our contusion SCI models, supporting TSD as a good biomarker for translating tissue damage thresholds from rat to cat. This observation suggests that such tissue level SPD and CDF may be used to produce a consistent SCI lesion in other animal models and to potentially fine-tune the degree of damage produced in the contusion SCI model.

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