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Editorial

Perspectives on the Role of Bioengineering in Neurotrauma Research

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We are very pleased to have served as guest editors for this special issue on Bioengineering in Neurotrauma Research. This assembly of articles was particularly challenging, as we tried to capture cutting-edge research across an extremely diverse and broad engineering discipline. According to the online Merriam-Webster dictionary, *bioengineering* is the "biological or medical application of engineering principles or engineering equipment, also called *biomedical engineering*." The topics of the articles in this issue range from novel studies of axon stretching and guided regeneration, to computer modeling and new image processing techniques.

In introducing this issue, we thought it would be of interest to put current research accomplishments in the context of history, as well as to anticipate future innovations. Although evidence of engineering influences in treating neurotrauma can be found as early as Neolithic times in the surgical practice of trephination to relieve symptoms of head injury (Levin et al., 1982; Granacher, 2007), the Renaissance period brought Galileo's mathematics and measurement devices to physicians, launching the beginning of medical engineering. The first use of the term *bioengineering* was not until c. 1955, however, when there was a growing need for better medical instrumentation, surgical advancements, replacement organs, and life support in space. This was also the era that witnessed the beginning of tissue culture (Gey et al., 1952), and the pioneering human tolerance experiments of Colonel Stapp (Stapp, 1948; Stapp and Gell, 1951). Intracranial pressure monitoring began during the 1950s as well, initiating modern neurocritical care (Marion 1999; Marshall, 2000). Today, bioengineering in neurotrauma research encompasses areas from biosensing to intraoperative magnetic resonance imaging (MRI).

Engineering applications to neurotrauma research can be seen in the use of cell and tissue preparations. Transection has been a model of injury since Galen accidently cut laryngeal nerves of a pig and Ramon y Cajal systematically cut axons (Ramon y Cajal, 1928). Biomechanics began to influence the field of cellular neurotrauma research in the 1990s (Ellis et al., 1995, Lucas and Wolf, 1991; Shepard et al., 1991), and over the next two decades, *in vitro* models became more sophisticated (Morrison et al., 1998; Kumaria and Tolias, 2008; Chen et al., 2009). In the present issue, Maguo and associates present a novel axonal injury system, addressing the need for even more high-throughput systems than most current systems can provide. Cullen and colleagues show the differences between loading mode of 3-D cultures, underlying the need to define input biomechanics. Elkin and co-workers use *in vitro* brain samples to study edema, lending mechanistic insight into the complex phenomenon of brain swelling, a basic yet critical physiological response to neural trauma. In addition to the study of cellular biomechanics and the acute injury response, cultures can be used to investigate regeneration of the damaged nervous system. The last three articles in this issue demonstrate different approaches to understanding growth cues and exploiting axogenesis for regenerative therapies. Voyiadjis and associates examine neurite outgrowth using novel microengineered channels and compare neurite preference to simulations based on predictive modeling. From the same group, Sundarataghavan and colleagues use microfluidics to guide neurites through 3-D collagen cultures, representing *in vivo*-like architecture. Loverde and co-workers present an innovative mechanical axon growth environment to slowly stretch axons and image growth and retraction in real time, providing a means to better understand tension-induced growth of axons.

The application of mechanics and finite element modeling to neural trauma has its roots in cadaver testing, from which the Wayne State Tolerance Curve was derived (see McLean and Anderson, 1997 for an account of the evolution of the biomechanics of traumatic brain injury [TBI] in the 20th century). In parallel, Denny-Brown and Russell proposed that a change in velocity would be required to cause brain damage (Denny-Brown and Russell, 1941). These and other studies led to the development of initial tolerance criteria, such as the Head Injury Criterion (HIC). Computer simulation capability has become much more advanced over the last two decades, and there is a need to use more accurate material properties for both human and animal studies. To this end, in the current issue Elkin and associates have measured the viscoelastic regional properties of juvenile and adult rat brain. Finite element models can also be used to better understand the

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relationship between stress/strain and tissue response. Pleasant and colleagues examined two different shaped impactor tips in the commonly used controlled cortical impact rodent model using both modeling and histology, correlating local strains with damage. In a separate article, Mao and co-workers use numerical analysis to map tissue strain for different cortical impact parameters, providing further mechanical explanation for the range of severities seen in experimental models.

Several other areas of engineering have contributed to advances in neurotrauma research. Imaging technology, for example, has come a long way since Roentgen developed x-ray imaging in 1896. Computed tomography (CT) and MRI were technological advancements that have led to improved diagnosis and treatment, followed by functional MRI and diffusion tensor imaging (DTI), advancements that are the fruit of engineering, radiology, and imaging processing progress. In this issue, a new application of multimodal segmentation of MR volumes is presented by Irimia and associates, with specific examples of how these techniques can be applied to human neuroimaging of bleeding, lesions, edema, and axonal injury following TBI.

As readers of neurotrauma research, we are acutely aware of the expansion of blast injury research in the past decade that has emerged from the higher survival rate among soldiers exposed to blasts (Fabrizio and Keltner, 2010). Cullen and colleagues present a novel dosimeter for blast exposure that is based on the structure and corresponding color changes of photonic crystals, and relate these measurements to brain pathology in the rat. Rafaels and co-workers use an animal model of blast to determine a fatality risk function that can be used to better understand blast modeling and brain tolerance.

In addition to studying injury mechanisms, neuroregenerative medicine is at the forefront of neurotrauma research, and can benefit from the fields of tissue engineering and neuroengineering. Since the first recorded brain graft in 1890 in a dog (Thompson, 1890), and encouraging results in spinal nerve electrical stimulation following spinal cord injury (SCI; Ellis, 1987), bioengineering has offered a myriad of approaches for neural regeneration. Aravamudhan and Bellamkonda present a review of several different strategies for repairing the damaged nervous system, and suggest that pharmaceutical and cell replacement methods should be considered along with interventions such as locomotor rehabilitation. As an example of new techniques in neural repair, Floyd and associates demonstrate that traditional scaffolding approaches can be adapted on the nano-level for improved control over repair following SCI.

As we have highlighted, bioengineering approaches influence nearly all areas of neurotrauma research, either directly or indirectly. Most of the injuries falling under the neurotrauma umbrella include complex physical loading of a very heterogeneous material, in both a morphological and functional context, which can be studied using multiscale biomechanics. Diagnostic methods such as imaging can provide a wealth of information about both structure and function. In addition, chemically- and physically-directed growth, using both *in vitro* and *in vivo* techniques, can assist with understanding regeneration and designing growth-promoting substrates. With the adoption of these and future techniques, bioengineering can become a common means to better study and control cells, validate diagnostics, and promote repair and regeneration. There is a strong appreciation for bioengineering within the neurotrauma community, and there is value in this positive interdisciplinary atmosphere, as we all move forward to solve problems facing patients, therapists, physicians, and researchers.

References

Chen, Y.C., Smith, D.H., and Meaney, D.F. (2009). In-vitro approaches for studying blast-induced traumatic brain injury. J. Neurotrauma 26, 861–876.

Denny-Brown, D., and Russell, W.R. (1941). Experimental cerebral concussion. Brain 64, 93–164.

Ellis, E.F., McKinney, J.S., Willoughby, K.A., Liang, S., and Povlishock, J.T. (1995). A new model for rapid stretch-induced injury of cells in culture: Characterization of the model using astrocytes. J. Neurotrauma 12, 325–339.

Ellis, W. (1987). Pulsed subcutaneous electrical stimulation in spinal cord injury: preliminary results. Bioelectromagnetics 8, 159–164.

Fabrizio, K.S., and Keltner, N.L. (2010). Traumatic brain injury in operation enduring freedom/operation iraqi freedom: a primer. Nurs. Clin. North Am. 45, 569–580, vi.

Gey, G.O., Coffman, W.D., and Kubicek, M.T. (1952). Tissue culture studies of the proliferative capacity of cervical carcinoma and normal epithelium. Cancer Res. 264–265.

Granacher, R.A. (2007). *Traumatic Brain Injury: Methods for Clinical & Forensic Neuropsychiatric Assessment*, 2nd ed. CRC: Boca Raton, FL.

Kumaria, A., and Tolias, C.M. (2008). In vitro models of neurotrauma. Br. J. Neurosurg. 22, 200–206.

Levin, H.S., Benton, A.L., and Grossman, R. (1982). Historical review of head injury, in: *Neurobehavioral Consequences of Closed Head Injury*. Oxford University Press: Oxford.

Lucas, J.H., and Wolf, A. (1991). In vitro studies of multiple impact injury to mammalian CNS neurons: prevention of perikaryal damage and death by ketamine. Brain Res. 543, 181–193.

Marion, D.W. (1999). Introduction, in: *Traumatic Brain Injury*. D.W. Marion (ed). Thieme: Stuttgart.

Marshall, L.F. (2000). Head injury: Recent past, present, and future. Neurosurgery 47, 546–561.

McLean, A.J., and Anderson, R.W.G. (1997). Biomechanics of closed head injury, in: *Head Injury*. P.Ra.R. Bullock (ed). Chapman & Hall: London.

Morrison, B. 3rd, Saatman, K.E., Meaney, D.F., and McIntosh, T.K. (1998). In vitro central nervous system models of mechanically induced trauma: a review. J. Neurotrauma 15, 911–928.

Ramon y Cajal, S. (1928). *Degeneration and Regeneration of the Nervous System*, 1st ed. Oxford University Press: Oxford.

Shepard, S.R., Ghajar, J.B.G., Giannuzzi, R, Kupferman, S., and Hariri, R.J. (1991). Fluid percussion barotrauma chamber: a new in vitro model for traumatic brain injury. J. Surg. Res. 51, 417–424.

Stapp, J.P. (1948). Problems of human engineering in regard to sudden declarative forces on man. Mil. Surg. 103, 99–102.

Stapp, J.P., and Gell, C.F. (1951). Human exposure to linear declarative force in the backward and forward facing seated positions. Mil. Surg. 109, 106–109.

Thompson, W.G. (1890). Brain grafting. Med. Bull. 12, 429–430.